STAPHYLOCOCCAL INFECTION OF THE NEWBORN IN HOSPITAL AND IN DOMICILIARY PRACTICE

T. F. ELIAS-JONES
M.B. Edin.
CONSULTANT PATHOLOGIST,
ILFORD AND BARKING HOSPITAL GROUP

I. GORDON
M.D. Edin., M.R.C.P., D.P.H.
AREA MEDICAL OFFICER AND MEDICAL OFFICER OF HEALTH, ILFORD

L. WHITTAKER
A.I.M.L.T.
SENIOR LABORATORY TECHNICIAN,
ILFORD AND BARKING HOSPITAL GROUP

With the assistance of the Ilford Health Visiting Staff

MORE and more outbreaks of serious staphylococcal infection among newborn infants in maternity units have been reported in recent years (Beaven and Burry 1956, Monro and Markham 1958). Some of these have been so severe that whole hospitals have had to close temporarily (Timbury et al. 1958). Less dramatic outbreaks are numerous (Shaffer et al. 1956, 1957), and, even in hospitals which are free from major incidents, diligent search will reveal cases of minor sepsis due to staphylococci (Forfar et al. 1953). The better hospitals are aware of this ever-present danger (Ravenholt and La Veck 1956); complacency and lack of proper facilities for investigation are usually found together.

Less is known about the incidence of this type of sepsis among infants born at home (Gairdner 1954). Our investigation was designed to compare this hazard in hospital and in domiciliary practice.

Scope of the Investigation

The survey was conducted in the borough of Ilford (pop. 180,000) from July, 1957, to June, 1958, by eighteen health visitors. Each health visitor assessed all infants she visited, and completed a standard questionary for each. All the health visitors were fully briefed before the start of the survey by two of us (I. G. and T. F. E.-J.). Criteria of infection were defined, likely sites of sepsis were named, and the importance of strict objectivity in assessment was stressed.

Material and Methods

When an infant showed signs of infection, the health visitor made a note of its nature and filled in the questionary; she then took the following swabs: (1) anterior nares (N), (2) umbilicus (U), (3) observed lesion(s) (L) (unless the lesion was in the nose or on the umbilicus). These were the "swabbed sepsis series".

After investigating and swabbing an infected child, the health visitor had to select, as soon as practicable, a clinically healthy infant to "match" the infected case as nearly as possible in age, sex, home conditions, &c. The standard questionary was completed for the "matched" infant, and two swabs (N and U) were taken. These comprised the "control series". (There were only 84 controls as against 98 infants in the "swabbed sepsis series".)

A third category emerged during the survey. These were infants who, though showing clinical signs of sepsis, were not swabbed for various reasons—e.g., antibiotic therapy begun before the health visitor's arrival; and certain lesions under intact skin (such as early paronychia) not ready for swabbing when first seen, but subsequent attempts to visit unsuccessful. These cases comprised our "unswabbed sepsis series" for which there are no bacteriological findings.

Bacteriological Methods

Each swab, within three or four hours, was thoroughly stirred in 5 ml. of nutrient broth from which, after sixteen to eighteen hours' incubation, subinoculations were made on horse-blood/agar plates which were incubated aerobically; staphylococci isolated were tested for coagulase production. If colonies obtained from one swab differed in pigmentation or other physical characteristics, representative colonies of each were selected and examined.

All coagulase-positive strains were tested, by the disc-diffusion technique, for their sensitivity to five antibiotics: penicillin (2·5 units per disc), erythromycin (1 μg. per disc), chloramphenicol (40 μg.), streptomycin (20 μg.), tetracycline (10 μg.); and to two chemotherapeutic agents—sulphafurazole (1 mg.) and nitrofurantoin (10 mg.), using *Staphylococcus aureus* (National Collection of Type Cultures 6571) as the test organism. In labelling a strain as "sensitive" or "resistant" we followed Edmunds et al. (1955), whose scheme of "resistance patterns" was used to distinguish between dissimilar strains. Finally, through the kindness of the director, a random sample of approximately a third of all strains isolated was phage-typed for us at the Staphylococcus Reference Laboratory, Colindale.

Results

CLINICAL FINDINGS

In the survey 1551 infants were visited, representing 70·8% of the "available infant population" from mid-1957 to mid-1958. The remaining 30% were "missed" for various reasons (mother and child staying with relatives in another area, &c.).

Of these 1551 infants, 275 (17·5%) were aged 8–13 days, 1224 (78·9%) were aged 14–20 days, 51 (3·3%) were aged 21–28 days, and 1 was aged 35 days. The overwhelming majority—1525 (98·4%), were between 10 and 21 days old.

Neonatal Sepsis and Place of Confinement

The main findings of the survey are summarised in table I. Of the 1129 infants born in hospital, 154 (13·6%) had septic lesions; the comparable figures for those born at home were 20 (4·8%) out of 414. Statistically the difference is highly significant ($\chi^2=23·5$, $P=<0·001$).

TABLE I—NEONATAL SEPSIS AND PLACE OF CONFINEMENT

Group of infants	Confinement		
	Hospital	Nursing-home	Domiciliary
With no signs of sepsis ..	975	8	394
With clinical evidence of sepsis:			
Swabbed	90 } 154 (13·6%)	..	9 } 20 (4·8%)
Not swabbed	64 }	..	11 }
Totals	1129	8	414

Seasonal Distribution of Sepsis

No seasonal influence on the incidence of sepsis was observed (table II).

Sex Incidence of Neonatal Sepsis

Table III shows that the incidence of sepsis among boys was 13·2%, and 9·0% among girls.

Incidence of Sepsis in Relation to Size of Family and Housing Conditions

Statistical analysis of the detailed figures obtained

TABLE II—SEASONAL DISTRIBUTION OF SEPSIS

Month of birth	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Total
Infants with no signs of sepsis	126	114	131	125	123	144	90	144	87	85	95	113	1377
Infants with clinical evidence of sepsis	8	13	13	12	30	20	14	15	12	15	13	9	174
Total	134	127	144	137	153	164	104	159	99	100	108	122	1551
Monthly sepsis rate (%)	6	10·2	9·0	8·8	19·6	12·2	13·5	9·4	12·1	15·0	12·0	7·4	11·21 p.a.
—	Spring			Summer			Autumn			Winter			
Total visited	405			454			362			330			1551
Infants with clinical evidence of sepsis: No.	34			62			41			37			174
% of total visited	8·4			13·6			11·3			11·2			

revealed no correlation between social conditions and the incidence of neonatal sepsis due to the staphylococcus.

Obstetrical Complications and Neonatal Sepsis

Among 1397 infants whose birth had been normal there were 151 cases of neonatal infection—an incidence of 10·8%. There were 154 infants whose births had been complicated in some way; and, of these, 23 had clinical evidence of sepsis, the incidence being 14·9%. The difference is not significant ($\chi^2=2·37$; P lies between 0·1 and 0·2).

TABLE III—SEX INCIDENCE

Group of infants	Sex of infants included in survey	
	Male	Female
With no signs of sepsis	709	668
With clinical evidence of sepsis	108 (*13·2%*)	66 (*9·0%*)
Total	817	734

The difference is highly significant ($\chi^2=6·937$, P = 0·01).

Type of Septic Lesions

The infections most often seen were:

1. Infections of the conjunctivæ and eyelids: 84 cases (48·3% of all infections, an incidence of 5·4% among all the newborn infants).
2. Skin lesions (septic blisters, boils, &c.): 61 cases (35% of all infections, a 3·8% incidence).
3. Umbilical infections: 30 cases (17·2% of all infections, a 1·9% incidence).

Other lesions encountered were: mastitis (7), paronychia (6), deep abscesses (2), discharging ears (2), and vulvitis (1); and 22 infants had coexisting infections of two distinct types.

We admit that not all the clinical sepsis in the unswabbed cases was necessarily due to staphylococci. But, while culture of the 430 swabs taken often yielded coagulase-negative staphylococci and other skin commensals, less than 10 yielded any potential pathogens (coliforms and proteus) other than coagulase-positive *Staph. aureus*, which was isolated from 207 swabs. It seems justifiable to regard neonatal infections encountered in this survey as staphylococcal.

TABLE IV—RESULTS OF SWABBING

—	Confinement							
	Hospital			Domiciliary			Combined hospital and domiciliary	
	Sepsis	Control	Totals	Sepsis	Control	Totals	Sepsis	Control
Swabbed	89	56	145	9	28	37	98	84
C.P.S. + swabs obtained *	71	32	103	5	10	15	76	42
% of total swabbed cases from which C.P.S. + swabs were obtained *	79·7	57·1	71	55·5	35·7	40·5	77·5	50

* C.P.S. + : coagulase-positive staphylococci grown on culture.

BACTERIOLOGICAL FINDINGS

Swabs Giving a Growth of Coagulase-positive Staphylococci

The main bacteriological findings are summarised in table IV. This shows that the presence of pathogenic staphylococci (in the tissues or on body surfaces) was bacteriologically proven in 77·5% of the infants with a clinical infection; but a 50% staphylococcal carrier-rate was also found among apparently healthy infants.

Of the swabbed cases, 71% of the infants delivered in hospital, but only 40·5% of those born at home, harboured pathogenic staphylococci. The difference is highly significant ($\chi^2=12·02$, P = <0·001). But the difference in carrier-rates between the two groups (57·1% in the hospital cases, and 35·7% in the domiciliary cases) is barely significant ($\chi^2=3·428$; P lies between 0·1 and 0·05). The conclusion is that 1 out of every 2 babies can expect—wherever he is born—to be colonised by pathogenic staphylococci by the age of 2–3 weeks; and those born in hospital run a much greater risk of acquiring *virulent* strains. In other words, clinical evidence of infection by these organisms in the baby born at home is much less likely.

TABLE V—SITES OF PATHOGENIC STAPHYLOCOCCI

Group	No. of infants with C.P.S. + swabs	Sites from which C.P.S. + swabs obtained			
		Nose	Umbilicus	Eye	Various septic lesions
Hospital:					
Sepsis	71	59	38	27	18
Control	32	32	12	..	..
Domiciliary:					
Sepsis	5	3	3	2	1
Control	10	8	4	..	..
Total	118	102	57	29	19

Sensitivity "Patterns" of Staphylococci Isolated

By using key patterns of sensitivity to antimicrobial agents to distinguish dissimilar strains, 130 separate strains of coagulase-positive staphylococci were identified among the 207 positive swabs obtained from 118 infants. Thus some of the infants were harbouring at least two different strains of pathogenic staphylococci.

114 of these 130 strains were found in infants born in hospital, and 16 in those born at home; 11 of those born in hospital and 1 born at home harboured two distinct strains.

As expected, resistance to penicillin was commonest; excluding 4 strains resistant to streptomycin alone, resistance to other antibiotics and/or sulphonamide was not encountered among penicillin-sensitive strains.

91 out of the 100 penicillin-resistant strains, and 94 out of all the 104 resistant strains, were from infants born in hospital. This reinforces the conclusion, already drawn from table IV, that the infant born in hospital is likelier to acquire a " dangerous " staphylococcus.

Sites from which Pathogenic Staphylococci were Cultured

In the light of the lesions described and their frequency, it follows from table V that many of the positive umbilical swabs—and all the positive nasal swabs—obtained in the sepsis series must have represented symptomless umbilical and nasal carriage by infants with active infections elsewhere. Clearly these two carrier-sites are potent autogenous sources for all kinds of neonatal infections.

Phage-typing

A random sample of 66 of the 207 strains of staphylococci isolated were submitted for phage-typing. 21 of these came from 21 different infants, and 45 from 20 other infants (2 each from 15, 3 each from 5). 4 of the 20 infants were each shown to be harbouring two distinct phage-types (and 1 probably three types) and 6 more were probably harbouring two types. All these 10 babies had been born in hospital (compare the results of sensitivity-pattern identification which was more fully investigated).

Phage-type 79 was identified in 17 infants, and type 52A/79 in 3, both types being common inhabitants of maternity units. Various phage-types were found among the other strains.

Discussion

These results differ from those published by some investigators in recent years.

Gairdner (1954) observed 230 infants born at home in Cambridge and found an infection-rate of 13%, while the infection-rate at the Cambridge Maternity Hospital during the same period (premature infants included) lay between 15% and 20%. Miller (1948) noted an infection-rate of 20% among 300 infants born at home in Newcastle upon Tyne, and the year before last (Miller 1959) reported a more recent survey in which 395 domiciliary births and 309 hospital births were compared: the sepsis-rate among the infants in the former group was 18% and in the latter 29%. Semple (1958) in Liverpool recorded an incidence of sepsis in infants born in hospital of 10·6% and in those born at home of 10·1%. Crosse and Mackintosh (1953) found a contrary trend, with a sepsis-rate of 14·48% in 1788 babies born at home in Birmingham, and only 10·48% among 1336 of those born in hospital.

Obviously the results obtained by different workers will be affected by the criteria they use to define an infection. Ours were deliberately chosen so that cases with the most trivial lesions were not overlooked, because even trivial infections are potentially dangerous (Forfar et al. 1953, Beaven 1958). Moreover, these criteria were the same for all the infants, irrespective of their place of birth; and they revealed that the sepsis-rate of 13·6%, after hospital confinement, compared very unfavourably with the 4·8% rate of the domiciliary group.

Our bacteriological findings broadly corroborate those of other workers (Ludlam 1953, Hurst 1957). Not only did we find that 71% of the infants delivered in hospital harboured pathogenic staphylococci, as against 40·5% of those born at home, but the majority of drug-resistant strains (e.g., 91% of the penicillin-resistant strains) were isolated from babies born in hospital. It is also noteworthy that 11 of the 145 infants born in hospital who were swabbed were found to be harbouring 2 distinct strains of coagulase-positive staphylococci, whereas this was proved in only 1 of 37 swabbed infants in the domiciliary group.

Such a state of affairs contributes to morbidity among the infants themselves when they are older (*Lancet* 1957); and it also tends to disseminate virulent strains of *Staph. aureus* in home circles (Wentworth et al. 1958).

The greater susceptibility of male infants to staphylococcal sepsis seems merely to reflect the sex difference in neonatal morbidity-rates from all causes. We found no evidence of an uneven seasonal distribution of neonatal infection, or of any relationship between sepsis in the infants and antecedent obstetrical complications. With regard to housing and family conditions, the staphylococcus appears to be no respecter of social status.

Clearly the efforts in many maternity units to minimise the spread of pathogenic staphylococci should be emulated and intensified everywhere. The necessary precautions have been detailed by Gillespie et al. (1958), Gillespie (1959), and others. Is it not time also that the communal nursery should cease to form part of the accommodation provided in a maternity unit?

It would be rash to attempt to tackle the problem by whittling down the list of commonly accepted obstetric indications for hospital confinement; but, when the choice of place of delivery is dictated solely by less substantial reasons, such as domestic or social convenience (Gordon et al. 1960), the relative freedom from risk of staphylococcal infection of the baby born at home must surely be considered. For those mothers who, for a valid reason, should be confined in hospital, the recently-canvassed idea of hospital confinement followed by lying-in at home has much to commend it. Not only would this offer the possibility that far more babies could escape to the comparative safety of their own homes before hospital staphylococci had colonised them, but also, by lessening overcrowding, it would reduce the bacterial population in the hospitals themselves.

Summary

1129 infants born in hospital and 414 born at home were examined for evidence of neonatal staphylococcal sepsis. Its incidence in the hospital group (13·6%) was significantly higher than in the domiciliary group (4·8%). Sepsis was significantly more prevalent in male infants. No seasonal fluctuations were observed; and social conditions or antecedent obstetric complications did not appear to influence the infection-rate. The infections were mainly minor ones; eye, skin, and umbilical infections (in that order) predominating.

Pathogenic staphylococci were isolated from 77·5% of infants with clinical infections; 50% of healthy control infants were also found to be staphylococcal carriers. 71% of the infants swabbed in the hospital group, and 40·5% in the domiciliary group, were shown to be harbouring these organisms. 90% of antibiotic-resistant strains found were isolated from infants born in hospital.

We are deeply indebted to Mr. E. H. Goatly of the borough treasurer's office, Ilford, for his invaluable help; to the borough treasurer for the use of a Hollerith sorting machine; and to Dr. R. E. O. Williams and Dr. Patricia Jevons for undertaking the phage-typing.

REFERENCES

Beaven, D. W. (1958) *Lancet*, i, 869.
— Burry, A. F. (1956) *ibid.* ii, 211.
Crosse, V. M., Mackintosh, J. M. (1953) *Brit. med. J.* i, 1374.
Edmunds, P. N., Elias-Jones, T. F., Forfar, J. O., Balf, C. L. (1955) *ibid.* i, 990.
Forfar, J. O., Balf, C. L., Elias-Jones, T. F., Edmunds, P. N. (1953) *ibid.* ii, 170.
Gairdner, D. (1954) Recent Advances in Pædiatrics. London.
Gillespie, W. A. (1959) *Lancet*, i, 246.
— Simpson, K., Tozer, R. C. (1958) *ibid.* ii, 1075.

References continued overleaf

EFFECT OF FOOD ON ABSORPTION OF RADIOACTIVE VITAMIN B_{12}

D. J. DELLER
M.B. Sydney, M.R.C.P., M.R.A.C.P.
NUFFIELD FOUNDATION DOMINION TRAVELLING FELLOW

H. GERMAR
M.D. Philippines
FELLOW OF THE INTERNATIONAL ATOMIC ENERGY AUTHORITY

L. J. WITTS
C.B.E., M.A. Oxon., M.D. Manc., Sc.D. Dubl, F.R.C.P.
NUFFIELD PROFESSOR OF CLINICAL MEDICINE

The Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford

VITAMIN-B_{12} absorption can be measured by determining the amount of radioactivity in the fæces (Heinle et al. 1952), the urine (Schilling 1953), the plasma (Booth and Mollin 1956), or over the liver (Glass et al. 1954), after an oral dose of radioactive vitamin B_{12}. In the conventional test, the tracer dose of radioactive vitamin B_{12} is given in the fasting state. Secretion of intrinsic factor may be depressed under these conditions and in some subjects, who absorb subnormal amounts of vitamin B_{12} when tested in this way, the parasympathetic stimulant carbamylcholine chloride (carbachol) increases absorption to normal (Mollin et al. 1957).

TABLE I—EFFECT OF FOOD ON ABSORPTION OF ^{58}Co VITAMIN B_{12} IN NORMAL SUBJECTS

Subject no.	Sex	Age	Diagnosis	Serum-vitamin B_{12} (μμg. per ml.)	Percentage fæcal excretion of 0·5 μg. ^{58}Co vitamin B_{12}	
					Fasting	With meal
1	M	29	Normal	1050	29	21
2	M	21	Normal	560	26	22
3	F	21	Normal	400	24	29
4	F	18	Normal	680	23	30
5	F	33	Normal	490	34	20
6	F	55	Gastric ulcer	650	30	24
7	M	60	Coronary occlusion	350	24	30
8	M	51	Coronary occlusion	400	23	17
9	M	42	Diabetes mellitus	1500	32	26
10	M	54	Glomerulonephritis	380	36	37

Radioactive vitamin B_{12} has been incorporated in pig and calf liver by parenteral injection of ^{60}Co vitamin B_{12}, and then given with a meal to normal subjects and to patients with pernicious anæmia (Reizenstein and Nyberg 1959). The liver preparations used have had only a small proportion of radioactive to total vitamin B_{12} and consequently the amount of vitamin B_{12} administered has been in excess of that dependent on the intrinsic-factor mechanism.

For the study of the effect of food on the absorption of physiological amounts of vitamin B_{12}, the simplest method is to give the tracer dose together with a vitamin-B_{12}-free meal. Swendseid et al. (1954), using a test dose of 0·5 μg. ^{60}Co vitamin B_{12}, observed increased absorption of vitamin B_{12} in four out of seven normal subjects when the test dose was given with a vitamin-B_{12}-free meal. Gräsbeck et al. (1956) found that when the oral dose was given 3 hours after a meal, the absorption of the vitamin was reduced; the vitamin-B_{12} content of the meal was not stated in this report.

In a recent study of vitamin-B_{12} absorption after partial gastrectomy, a number of subjects were found with a low vitamin-B_{12} level in the serum but with normal vitamin-B_{12} absorption in the fasting state. On the analogy of iron, it was thought that an abnormality of absorption of vitamin B_{12} might be found if the tracer dose was given with food. Iron absorption after gastric operations is normal when iron is administered to the fasting patient as the ferrous salt (Smith and Mallett 1957, Baird et al. 1957), but it is impaired when the iron is given during, or incorporated in, a meal (Chodos et al. 1957, Pirzio-Birolo et al. 1958, Baird and Wilson 1959, Choudhury and Williams 1959). The absorption of vitamin B_{12} after gastric resection, however, was found to be improved with food in the experiments reported here.

TABLE II—EFFECT OF INTRINSIC FACTOR AND OF FOOD ON ABSORPTION OF ^{58}Co VITAMIN B_{12} IN PERNICIOUS ANÆMIA

Patient no.	Sex	Age	Percentage fæcal excretion of 0·5 μg. ^{58}Co vitamin B_{12}		
			Fasting	With intrinsic factor	With food
11	M	44	80	35	84
12	M	44	85	42	89
13	F	51	88	24	88
14	F	79	98	44	94
15	F	76	78	38	68

Material and Methods

The control group consisted of five healthy volunteers and five hospital inpatients with diseases not associated with disturbance of absorption of vitamin B_{12} (table I). Five patients with pernicious anæmia in remission were investigated; they received no vitamin B_{12} for at least a week before and during the period of study (table II). Twenty-one patients who had had a partial gastrectomy for peptic ulcer 1–18 years previously were studied (table III). These patients were selected from a larger group of

TABLE III—EFFECT OF INTRINSIC FACTOR AND OF FOOD ON ABSORPTION OF ^{58}Co VITAMIN B_{12} AFTER PARTIAL GASTRECTOMY

Patient no.	Sex	Age	Type of gastrectomy	Time since gastrectomy (yr.)	Serum-vitamin B_{12} (μμg. per ml.)	Fæcal fat (g. per day)	Percentage fæcal excretion of 0·5 μg. ^{58}Co vitamin B_{12}		
							Fasting	With intrinsic factor	With food
16	F	31	Polya	4	160	5·7	87	54	83
17	F	55	Billroth I	8	140	14·4	83	15	16
18	M	58	Polya	5	120	15·7	72	11	49
19	M	58	Polya	11	140	20·4	70	39	67
20	F	71	Polya	11	80	7·5	66	17	22
21	M	59	Polya	15	210	6·2	63	30	35
22	M	59	Polya	13	75	8·9	54	62	51
23	F	43	Polya	3	150	7·3	53	15	11
24	M	50	Billroth I	10	95	9·7	51	20	13
25	M	57	Polya	12	250	5·8	50	26	13
26	F	44	Polya	2	130	7·0	46	..	10
27	F	69	Polya	10	100	12·1	38	..	26
28	M	49	Polya	9	90	4·1	38	..	20
29	M	41	Polya	9	200	5·8	36	..	6
30	F	52	Billroth I	3	140	10·2	34	..	12
31	M	53	Polya	9	320	5·2	34	..	24
32	M	38	Polya	11	120	4·9	33	..	15
33	F	54	Polya	1	960	11·6	30	..	16
34	F	35	Billroth I	10	85	5·2	25	..	34
35	M	61	Polya	18	95	16·6	20	..	19
36	F	39	Billroth I	10	630	5·2	20	..	17

The cases are arranged beginning with those in which the fasting absorption of vitamin B_{12} is most greatly impaired.

DR. ELIAS-JONES & OTHERS: REFERENCES—*continued*

Gordon, I., Elias-Jones, T. F., Ilford health visiting staff (1960) *Brit. med. J.* i, 52.
Hurst, V. (1957) *J. Hyg., Camb.* **55**, 299.
Lancet (1957) i, 205.
Ludlam, G. B. (1953) *J. Hyg., Camb.* **51**, 64.
Miller, F. J. W. (1948) Personal communication. Cited by Gairdner (1954); p. 105.
— (1959) *Brit. med. J.* ii, 425.
Monro, J. A., Markham, N. P. (1958) *Lancet*, ii, 186.
Ravenholt, R. T., La Veck, G. D. (1956) *Amer. J. publ. Hlth*, **46**, 1287.
Semple, A. B. (1958) Annual report of the medical officer of health for Liverpool for 1958.
Shaffer, T. E., Baldwin, J. N., Rheins, M. S., Sylvester, R. F. (1956) *Pediatrics, Springfield*, **18**, 750.
— Sylvester, R. F., Baldwin, J. N., Rheins, M. S. (1957) *Amer. J. publ. Hlth*, **47**, 990.
Timbury, M. C., Wilson, T. S., Hutchison, J. G. P., Govan, A. D. T. (1958) *Lancet*, ii, 1081.
Wentworth, F. H., Miller, H. L., Wentworth, B. B. (1958) *Amer. J. publ. Hlth*, **48**, 287.

those with partial gastrectomy, in which vitamin-B_{12} absorption tests had been performed, because they demonstrated a range of absorption from normal to that degree of impairment found in patients with pernicious anæmia or after total gastrectomy. Ten of the twenty-one patients had impaired absorption of vitamin B_{12}, 50% or more of the test dose being excreted. The serum-vitamin-B_{12} level was below the lower limit of normal (150 μμg. per ml.) in thirteen of them.

Absorption of ^{58}Co-labelled vitamin B_{12}

0·5 μg. ^{58}Co-labelled vitamin B_{12}, obtained from the Radiochemical Centre, Amersham (specific activity 1·2–2·0 μC per μg.), was given by mouth in 200 ml. of water after a 12-hour fast, and nothing further was allowed for 3 hours. Stools were collected in waxed-cardboard containers for 1 week, and the fæcal radioactivity was measured in a ring counter made up of 32 Geiger-Müller tubes in parallel. Fæcal radioactivity was measured until the activity in each of 2 consecutive days' collection was less than 1% of the dose administered. The difference between the amount of radioactivity given by mouth and the fæcal excretion measured was taken to be the amount of vitamin B_{12} absorbed.

The fæcal excretion of radioactivity in 82 tests on sixty normal subjects in this laboratory has been 9–46% of the oral

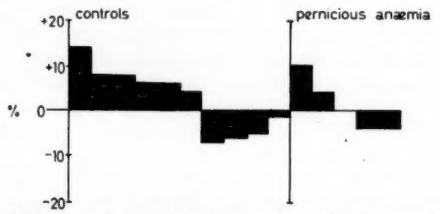


Fig. 1—Differences between fæcal excretion of ^{58}Co vitamin B_{12} after fasting and with food in control subjects and in pernicious anæmia. Differences expressed as percentage of oral dose administered.

dose administered, with a mean of 28% and standard deviation of 9%. The difference in the fæcal excretion in 94 duplicate tests has ranged from 0–22% of the administered dose with a mean difference of 7% and standard deviation of 6%. A difference of more than 19% in 2 successive tests on the same person is significant at $P = < 0{\cdot}05$.

At least 2 tests were carried out on each subject, 1 in which 0·5 μg. ^{58}Co-labelled vitamin B_{12} was administered fasting and 1 in which it was given with a standard vitamin-B_{12}-free meal. If the absorption of vitamin B_{12} in the fasting state was impaired, a 3rd test was carried out in which the tracer dose of vitamin B_{12} was given together with intrinsic factor. Intrinsic factor (50 mg. Lederle 45774–133, or 10 mg. Lederle, W.E.S. 818) was mixed with the test dose of radioactivity and given to the subject in the fasting state. The order of testing was randomised as far as possible, and successive tests in the same subject were usually done at intervals of not less than 2 weeks.

To test the reproducibility of the results, 10 vitamin-B_{12}-absorption tests were repeated. The differences in fæcal excretion of radioactivity between the 2 tests in the ten subjects ranged from 0–9% with a mean difference of 4% and standard deviation of 3%.

Vitamin-B_{12}-free Meal

The patients had an ordinary breakfast and the vitamin-B_{12}-free meal was given as lunch about 1 P.M. It consisted of a mixed vegetable risotto, pears, coffee, and orange squash, and provided 750 Calories and 30 g. fat. 0·5 μg. ^{58}Co-labelled vitamin B_{12} was added to 50 ml. of orange squash and diluted with 150 ml. of water. This was drunk intermittently during the meal and finished by the end of the risotto. Water was added to the glass and drunk, and this procedure repeated.

Serum-vitamin B_{12}

The serum level of vitamin B_{12} was assayed using *Lactobacillus leichmannii* as the test organism (Spray 1955). Normal

TABLE IV—STATISTICAL SIGNIFICANCE OF THE DIFFERENCES BETWEEN MEAN ABSORPTION OF ^{58}Co VITAMIN B_{12}, FASTING AND WITH FOOD

Group of subjects	^{58}Co-vitamin B_{12} test	Mean fæcal excretion as % oral dose	Significance of difference between means
Controls	Fasting	28	$P > 0{\cdot}1$
	With food	26	
Pernicious anæmia	Fasting	86	$P > 0{\cdot}1$
	With food	85	
Partial gastrectomy (all patients)	Fasting	48	$P < 0{\cdot}001$
	With food	27	
Partial gastrectomy (no. 16–25)	Fasting	65	$P < 0{\cdot}001$
	With food	35	
Partial gastrectomy (no. 26–36)	Fasting	32	$P < 0{\cdot}01$
	With food	18	

subjects have a vitamin-B_{12} concentration in the range of 150–1000 μμg. per ml. (mean 450 μμg.) and patients with pernicious anæmia a value below 150 μμg. (Spray and Witts 1958).

Fæcal Fat

Stools were collected for a period of 4 days, and fæcal fat estimated by the method of van de Kamer et al. (1949). The subjects took their normal diet during this period. Normal subjects in this laboratory excrete less than 7·0 g. of fat a day when this technique is used.

Results

100 absorption tests with ^{58}Co-labelled vitamin B_{12} were performed on thirty-six subjects, each subject having the test fasting and with food. Fifteen subjects had the test done with intrinsic factor, three with orange squash but without the vitamin-B_{12}-free meal, and 10 absorption tests were repeated.

Controls

In control subjects, the fæcal excretion of radioactivity after 0·5 μg. ^{58}Co-labelled vitamin B_{12} was 23–36% of the oral dose in the fasting test and 17–37% when the test dose was administered with the standard meal (table I). The differences in fæcal excretion of radioactivity between the fasting and the food test, expressed as a percentage of the oral dose of radioactivity administered, were +14% to −7% (fig. 1). There was no significant difference between the means in the fæcal excretion value of the two groups (table IV).

Pernicious Anæmia

Patients with pernicious anæmia excreted 78–98% of the test dose in fasting state and 68–94% with the standard meal (table II). Administration of intrinsic factor reduced the fæcal excretion of radioactivity to

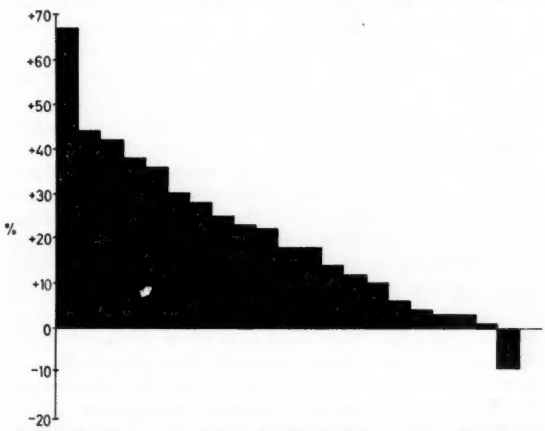


Fig. 2—Differences between fæcal excretion of ^{58}Co vitamin B_{12} after fasting and with food in 21 patients who had undergone partial gastrectomy.

24–44% of the dose given. The differences in fæcal excretion between the fasting and food tests were +10 to −4% of the oral test dose (fig. 1). The difference between the means of the fæcal excretion after fasting and with intrinsic factor was statistically significant ($P < 0.001$), but the difference between the fasting test and food test was not significant (table IV).

Partial Gastrectomy

Fæcal excretion of radioactivity in the gastrectomy group was 20–87% of the oral dose under fasting conditions, 6–83% with the standard meal, and in ten patients given intrinsic factor with the test dose, 11–62% (table III).

Twenty out of twenty-one patients absorbed more vitamin B_{12} when it was given with food (fig. 2). The increase in absorption in ten patients was more than 20% of the amount administered. Statistical analysis shows that the increased absorption of vitamin B_{12} after food is significant, whether all gastrectomy cases are considered together or whether they are divided into those whose fasting absorption is normal and those in whom it is impaired (table IV). The difference in absorption between vitamin B_{12} given with intrinsic factor and vitamin B_{12} given with food in patients 16–25 was not significant ($P > 0.1$). The difference between the means for the excretion of vitamin B_{12} given with food in the controls (26%) and patients 26–36 with partial gastrectomy (18%) is just significant at $P < 0.05$. In the only three subjects tested the absorption of vitamin B_{12} was not significantly enhanced by orange squash without the vitamin-B_{12}-free meal.

The level of vitamin-B_{12} in the serum was subnormal in thirteen of the patients who had undergone partial gastrectomy and enhanced absorption of vitamin B_{12} with food was observed in some cases in this group. The enhancement of absorption with food did not seem to be correlated with the presence or absence of steatorrhœa after partial gastrectomy.

Discussion

This study has shown that the absorption of radioactive vitamin B_{12} after partial gastrectomy may be significantly enhanced when the test dose is given with a vitamin-B_{12}-free meal. In patients with partial gastrectomy, in whom absorption of vitamin B_{12} is subnormal under fasting conditions and can be corrected by intrinsic factor, the mean improvement in absorption after food is comparable to the effect of intrinsic factor. Food likewise enhances the mean percentage absorption of vitamin B_{12} in patients after gastrectomy whose fasting absorption is within the normal range. This effect of food was not observed in normal subjects or patients with pernicious anæmia.

The absorption of vitamin B_{12} is increased by various methods. Swendseid et al. (1954) attributed the enhanced absorption of vitamin B_{12} in four subjects when the test dose was given with a vitamin-B_{12}-free meal to stimulation of secretion of intrinsic factor by food. Carbachol likewise appears to improve vitamin-B_{12} absorption by stimulating the secretion of intrinsic factor (Mollin et al. 1957). Normal subjects and patients with pernicious anæmia have been shown to absorb more vitamin B_{12} if it is administered as ^{60}Co-labelled vitamin B_{12} incorporated in liver rather than as a comparable solution of the crystalline radiovitamin (Reizenstein and Nyberg 1959). It is not, however, possible to ascribe this enhancing effect of liver to stimulation of secretion of intrinsic factor, as doses of vitamin B_{12} were used which are larger than those dependent on intrinsic factor for absorption (Baker and Mollin 1955).

Another agent which has been reported to enhance absorption of vitamin B_{12} is *d*-sorbitol, a hexahydric alcohol. Chow et al. (1958) observed a greater absorption of vitamin B_{12} in normal persons when the test dose of radioactivity was given with *d*-sorbitol than when given with an inert control mixture. In the intact rat, vitamin-B_{12} absorption is enhanced not only by *d*-sorbitol, but by *d*-mannitol, *d*-xylose, 'Tween 80', and 'Tween 85' (Greenberg et al. 1957, Okuda et al. 1960). *d*-Sorbitol, however, has no effect in promoting vitamin-B_{12} absorption in patients unable to secrete intrinsic factor (Ellenbogen et al. 1958). In our patients orange squash alone did not improve the absorption of vitamin B_{12}, but the separate effect of other components of the meal was not investigated.

The improvement in absorption with these agents may be due to delay in gastric emptying or intestinal transit so that more time is provided for the vitamin to mix with intrinsic factor and to be bound to the intestinal receptors (Okuda et al. 1960). Herbert (1959) suggested that two mechanisms whereby an added agent might enhance vitamin-B_{12} absorption in the normal subject were: (1) stimulation of intrinsic-factor secretion, and (2) the formation of a bond with the vitamin which is only broken in the small intestine. Food may provide such a stimulus to intrinsic-factor secretion and it may also act as a bond which protects the vitamin.

There is evidence that though the stomach is responsible for the secretion of intrinsic factor it may paradoxically exert an inhibitory influence on vitamin-B_{12} absorption. In normal subjects absorption of ^{60}Co-labelled vitamin B_{12} is significantly greater after instillation of the dose into the duodenum than after oral administration (Citrin et al. 1957). Johnson and Berger (1958) using ^{60}Co-labelled vitamin B_{12} in timed-release capsules demonstrated greater absorption of the vitamin from the small intestine than from the stomach. In some patients after total gastrectomy the absorption of vitamin B_{12}, when the test dose of radioactivity is given with a source of intrinsic factor, is greater than that shown either by normal persons or by patients with pernicious anæmia given a source of intrinsic factor with the test dose (Halsted et al. 1954). This may be the reason that the enhancement of absorption of vitamin B_{12} with food is seen only in partial gastrectomy. In patients 26–36 where sufficient intrinsic factor was available to promote normal absorption of vitamin B_{12}, the mean absorption with food was 82% as compared with 74% in the controls with intact stomachs. The difference is only just significant, and, in any event, it is not satisfactory to compare a selected group of patients with partial gastrectomy with unselected controls.

Summary

Absorption of vitamin B_{12} was measured in normal subjects, patients with pernicious anæmia, and patients who had undergone partial gastrectomy. A dose of ^{58}Co-labelled vitamin B_{12} was given by mouth, both under fasting conditions and with a vitamin-B_{12}-free meal, and the radioactivity excreted in the fæces was determined.

In patients who had undergone partial gastrectomy the absorption of ^{58}Co-labelled vitamin B_{12} was significantly enhanced when the test dose was given with food. The effect was not constant though it took place at all levels of

absorption of vitamin B_{12}. In some patients in whom the absorption of vitamin B_{12} was grossly subnormal, the effect of food was comparable with that of intrinsic factor.

The enhancing effect of food was not observed in normal subjects or in patients with pernicious anæmia.

The mechanism of the enhancement of the absorption of labelled vitamin B_{12} by food after partial gastrectomy is contrasted with the action of food in diminishing the absorption of labelled iron after partial gastrectomy.

The administration of a fasting dose of radioactive vitamin B_{12} is not a reliable method of determining the ability of the patient to absorb vitamin B_{12} after partial gastrectomy.

We are indebted to Mr. B. O. Bartlett of the unit of Biometry, University of Oxford, for statistical analyses, and to Miss R. E. Longstaff and the dietitian's department of the Radcliffe Infirmary, Oxford, for the preparation of the vitamin-B_{12}-free meal. This work was in part supported by a grant to Prof. L. J. Witts from the Medical Research Council.

REFERENCES

Baird, I. M., Podmore, D. A., Wilson, G. M. (1957) *Clin. Sci.* **16**, 463.
— Wilson, G. M. (1959) *Quart. J. Med.* **28**, 35.
Baker, S. J., Mollin, D. L. (1955) *Brit. J. Hæmat.* **1**, 46.
Booth, C. C., Mollin, D. L. (1956) *ibid.* **2**, 223.
Chodos, R. B., Ross, J. F., Apt, L., Pollycove, M., Halkett, J. A. E. (1957) *J. clin. Invest.* **36**, 314.
Choudhury, M. R., Williams, J. (1959) *Clin. Sci.* **18**, 527.
Chow, B. F., Meir, P., Free, S. M. (1958) *Amer. J. Clin. Nutr.* **6**, 30.
Citrin, Y., de Rosa, C., Halsted, J. A. (1957) *J. Lab. clin. Med.* **50**, 667.
Ellenbogen, L., Herbert, V., Williams, W. L. (1958) *Proc. Soc. exp. Biol., N.Y.* **99**, 257.
Glass, G. B. J., Boyd, L. J., Gellin, G. A., Stephanson, L. (1954) *Arch. Biochem.* **51**, 251.
Gräsbeck, R., Nyberg, W., Siurala, M. (1956) *Nord. Med.* **56**, 1656.
Greenberg, S. M., Herndon, J. F., Rice, E. G., Parmelee, E. T., Gulesich, J. J., van Loon, E. J. (1957) *Nature, Lond.* **180**, 1401.
Halsted, J. A., Gasster, M., Drenick, E. J. (1954) *New Engl. J. Med.* **251**, 161.
Heinle, R. W., Welch, A. D., Scharf, V., Meacham, G. C., Prusoff, W. H. (1952) *Trans. Ass. Amer. Phycns.* **65**, 214.
Herbert, V. (1959) The Megaloblastic Anæmias. New York.
Johnson, P. C., Berger, E. S. (1958) *Blood*, **13**, 457.
Mollin, D. L., Booth, C. C., Baker, S. J. (1957) *Brit. J. Hæmat.* **3**, 412.
Okuda, K., Duran, V. E., Chow, B. F. (1960) *Proc. Soc. exp. Biol., N.Y.*, 103, 588.
Pirzio-Biroli, G., Bothwell, T. H., Finch, C. A. (1958) *J. Lab. clin. Med.* **51**, 37.
Reizenstein, P. G., Nyberg, W. (1959) *Lancet*, ii, 248.
Schilling, R. F. (1953) *J. Lab. clin. Med.* **42**, 860.
Smith, M. D., Mallett, B. (1957) *Clin. Sci.* **16**, 23.
Spray, G. H. (1955) *ibid.* **14**, 661.
— Witts, L. J. (1958) *Brit. med. J.* i, 295.
Swendseid, M. F., Gasster, M., Halsted, J. A. (1954) *Proc. Soc. exp. Biol., N.Y.* **86**, 834.
van de Kamer, J. H., Huinink, H. ten B., Weyers, H. A. (1949) *J. biol. Chem.* **177**, 347.

CARCINOID SYNDROME

Serotonin Release Induced with Intravenous Adrenaline or Noradrenaline

W. S. PEART
M.D. Lond., F.R.C.P.
PROFESSOR OF MEDICINE IN THE UNIVERSITY OF LONDON

T. M. ANDREWS
B.Sc. Lond.
MEDICAL STUDENT

J. I. S. ROBERTSON
M.B., B.Sc. Lond., M.R.C.P.
LECTURER IN MEDICINE

ST. MARY'S HOSPITAL LONDON, W.2

IN a previous paper (Peart et al. 1959) we reported that in patients with the carcinoid syndrome typical facial flushes could be provoked with small intravenous doses of adrenaline or noradrenaline. There and elsewhere (Robertson et al., in preparation), we have given reasons for believing that, though humorally mediated, the flushing attacks are not due to the release of serotonin into the general circulation. The possibility, of course, remains that serotonin release might take place in some patients during a flush, though hitherto there has been no convincing demonstration of a rise in either the free or total plasma-serotonin during an attack. Several cases have been described (Thorson 1956, Schneckloth et al. 1959) in which overbreathing has been noted during the flushing attacks, and in these patients, release of serotonin—a known respiratory stimulant—might well occur. We have recently had the opportunity of studying such a patient, and have been able to show a rise in the level of free plasma-serotonin during facial flushes induced with either adrenaline or noradrenaline. There are, nevertheless, powerful objections to the acceptance of this rise in the free plasma-serotonin as the sole cause of the flushing. A preliminary account of the present study has already been published (Andrews et al. 1960).

Case-report

In June, 1958, a married woman, then aged 57, began to have attacks of central abdominal pain lasting 6–8 minutes. At about the same time she had diarrhœa, passing watery stools every $^1/_2$–1 hour. She had had facial flushes from the time of the menopause in 1947; these had been more frequent and more severe since early 1958, from which time she had also noticed wheezing and dyspnœa on exertion.

In October, 1958, she had symptoms and signs of acute intestinal obstruction, and at an operation performed on Oct. 30 by Mr. E. E. O'Malley a small-gut obstruction due to an annular growth of the ileum was found three feet from the ileo-cæcal junction. There were tumour deposits in the local lymph-nodes, and the liver was studded with metastatic deposits. The ileal neoplasm was resected and an end-to-end anastomosis was made. Histological sections showed typical appearances of a carcinoid tumour.

In November, 1959, the patient was seen to have frequent attacks of facial flushing, though many of the minor ones were unnoticed by her. There were several telangiectases on the forehead, cheeks, and nose. She was dyspnœic on the slightest exertion, and numerous rhonchi, mainly expiratory, were audible over the entire chest. No cardiac lesion was detectable clinically. The liver was grossly enlarged to well below the umbilicus and was slightly tender on compression. Several nodules were clearly palpable.

The 24-hour urinary output of 5-hydroxyindole acetic acid varied between 99 and 306 mg. (normal upper limit 10 mg.).

Investigations

Severe attacks of facial flushing were induced by the intravenous injection of 2 μg. of adrenaline or 10 μg. of noradrenaline.

Single intravenous injections of serotonin-creatinine sulphate in doses from 0·04 mg. to 1·5 mg. (in terms of the base), as well as infusions at different rates, failed to reproduce facial flushes of either the type or the severity seen in spontaneous attacks or in those induced with adrenaline or noradrenaline. The flushes following the injection of the larger quantities of serotonin were more cyanotic than those following adrenaline or noradrenaline, and were restricted to the tip of the nose and the area around the mouth, the rest of the facial skin being predominantly pale. The subjective sensations following these injections of large quantities of serotonin were not felt in the spontaneous or induced flushes; tingling in the nose and mouth, with severe hyperpnœa, were prominent after serotonin. Some overbreathing was, however, seen during the flushes provoked with adrenaline or noradrenaline, suggesting that release of serotonin, though in quantities too small to account for the flush, might have taken place.

Under local anæsthesia, a no. 9 U.S.A. cardiac catheter was passed from an antecubital vein until the tip was seen on fluoroscopy to lie in a hepatic vein. Rapid serial blood samples were taken during flushes provoked by intravenous adrenaline or noradrenaline. In all, four attacks were induced (see table).

The free plasma-serotonin was assayed biologically on the fundal strip of the rat's stomach (Vane 1957) using the technique we have described elsewhere (Robertson and Andrews 1961). As the table and the figures show, both adrenaline and noradrenaline could release a substance responsible

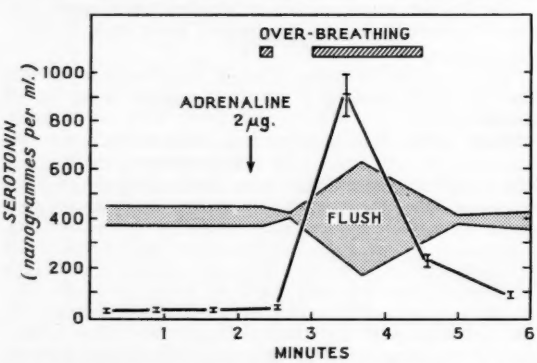
FREE PLASMA-SEROTONIN LEVELS AFTER PROVOKING DOSE OF ADRENALINE OR NORADRENALINE

No.	Provoking dose	Site of samples	Free plasma-serotonin levels (ng. per ml.)		
			Resting	Peak level during flush	Final level measured
1	2 μg. adrenaline	Hepatic vein	20–30	600–800	50–66
2	2 μg. adrenaline	Upper inferior vena cava	20–30	320–400	50–60
3	10 μg. noradrenaline	Hepatic vein	30–40	440–480	64–72
4	2 μg. adrenaline	Hepatic vein	24–32	830–1000	75–100

for an increase in plasma activity. This substance was shown to be indistinguishable from serotonin. The response was unaffected by the addition of atropine sulphate (10^{-7}) and mepyramine maleate (2×10^{-7}) to the assay bath, but was virtually abolished by 2-bromo-lysergic acid diethylamide (10^{-6}). The activity remained after preliminary extraction of the plasma with acetone, and the active fraction was indistinguishable from serotonin on paper-electrophoresis.

Discussion

Serotonin release by adrenaline or noradrenaline has a parallel in the release of catechol amines from adrenal medullary tumours by intravenous histamine (Roth and Kvale 1945). Further, it has been shown that serotonin will release histamine from living tissues (Feldberg and Smith 1953), and it has also been suggested that serotonin will release adrenaline from the adrenal medulla of the cat (Reid 1952). Amin et al. (1954) have shown that the distribution of serotonin in the brain follows closely the distribution of noradrenaline, and Brodie and Shore (1957) have developed the concept of serotonin as the chemical transmitter of the central parasympathetic system, with noradrenaline as the central sympathetic transmitter. The present observation is of considerable interest in these connections. A demonstration that a similar relation between catechol amines and serotonin exists in normal physiological processes might have wide significance.



Free plasma-serotonin levels in hepatic vein samples taken during a flush provoked by 2 μg. of adrenaline.

The horizontal bars indicate the bracket limits between which the value for each estimation lay. The shaded area indicates diagrammatically the depth of the flush, which was recorded by serial colour photographs.

Summary

In the carcinoid syndrome, typical facial flushes may be provoked by small intravenous doses of adrenaline or noradrenaline. Some workers have suggested that these attacks are due to the release of serotonin into the general circulation.

In a patient with carcinoidosis, confirmed at operation, repeated single intravenous injections of serotonin-creatinine sulphate in doses between 0·04 mg. and 1·5 mg., as well as infusions of serotonin at different rates, failed to reproduce the typical facial flushes of a spontaneous attack. The flushes also differed from those provoked by adrenaline or noradrenaline.

Samples of blood from a hepatic vein or from the vena cava, taken during flushes provoked by adrenaline or noradrenaline, showed an increased plasma-serotonin level.

Serotonin may be the chemical transmitter of the central parasympathetic system, with noradrenaline as the central sympathetic transmitter. The present observation is of interest in this connection, and it might be of great significance if a similar relation could be shown between the catechol amines and serotonin in normal physiological processes.

We are greatly indebted to the patient for her willing cooperation in this work. We also thank Dr. J. R. Ellis for permission to study the case.

REFERENCES

Amin, A. H., Crawford, T. B. B., Gaddum, J. H. (1954) *J. Physiol.* **126,** 596.
Andrews, T. M., Peart, W. S., Robertson, J. I. S. (1960) *ibid.* **155,** 81.
Brodie, B. B., Shore, P. A. (1957) *Ann. N.Y. Acad. Sci.* **66,** 631.
Feldberg, W., Smith, A. N. (1953) *Brit. J. Pharmacol.* **8,** 406.
Peart. W. S., Robertson, J. I. S., Andrews, T. M. (1959) *Lancet*, ii, 715.
Reid, G. (1952) *J. Physiol.* **118,** 435.
Robertson, J. I. S., Andrews, T. M. (1961) *Lancet*, i, 578.
— Peart, W. S., Andrews, T. M. In preparation.
Roth, G. M., Kvale, W. F. (1945) *J. Lab. clin. Med.* **30,** 366.
Schneckloth, R. E., Page, I. H., Corcoran, A. C. (1959) *Circulation*, **19,** 766.
Thorson, A. H. (1956) *Amer. Heart J.* **52,** 444.
Vane, J. R. (1957) *Brit. J. Pharmacol.* **12,** 344.

FREE SEROTONIN IN HUMAN PLASMA

Quantitative and Qualitative Estimation

J. I. S. ROBERTSON
M.B., B.Sc. Lond., M.R.C.P.
LECTURER IN MEDICINE

T. M. ANDREWS
B.Sc. Lond.
MEDICAL STUDENT

ST. MARY'S HOSPITAL, LONDON, W.2

A CONSIDERABLE problem in the investigation of carcinoid disease has been the difficulty in measuring accurately the level of serotonin (5-hydroxytryptamine, 5-H.T.) circulating free in the plasma.

Though it seems likely that the free plasma-serotonin, rather than that bound to the platelets, is the biologically active fraction (Magalini and Stefanini 1956), several workers have estimated either the serum-serotonin or the whole-blood serotonin as a measure of the circulating amine (Pernow and Waldenström 1957, Sjoerdsma et al. 1957). The losses involved in allowing blood to clot are considerable and variable (Zucker and Borelli 1955, Hardisty and Stacey 1955), and small, but possibly significant, changes in the level of serotonin may be masked in this procedure. When attempts have been made to measure separately the free and platelet-bound serotonin, such widely differing methods have been used by various workers that the results obtained by different groups are rare comparable. Lengthy extraction procedures must often involve considerable losses, and the methods of estimation finally used have varied widely in sensitivity and specificity. In carcinoidosis, large quantities of serotonin are carried in the blood-platelets, and the breakdown of quite a small proportion of the platelets in the collection of the sample could readily raise the estimated value for free serotonin to falsely high levels. Some of the values given for the free plasma-serotonin in carcinoid disease have been remarkably high (Goble et al. 1955). Alternatively, free plasma-serotonin could be picked up by the

platelets, and this process would be particularly rapid at 37°C (Hardisty and Stacey 1955).

The method described here was evolved by us in an attempt to obtain comparable measurements of the free plasma-serotonin from patient to patient with carcinoid disease. In particular, we were concerned with serotonin estimations on plasma samples obtained in rapid succession during attacks of facial flushing in the carcinoid syndrome.

The following considerations we regarded important: (1) to avoid the losses inherent in lengthy extraction procedures the plasma should be assayed neat; (2) the assay should be reasonably specific for serotonin, and should be suitable for detecting rapid changes in plasma activity; and (3) platelet breakdown, with consequent release of serotonin, should be avoided as far as possible, and the uptake of free plasma-serotonin by intact platelets minimised.

The most sensitive method at present available for the measurement of serotonin is biological assay using the fundal strip of the rat's stomach (Vane 1957). This preparation will consistently respond to quantities of serotonin as small as 1·0 ng. (10^{-9} g.) and, under favourable conditions, 0·1 ng. We have found this an accurate and sensitive quantitative technique.

For more precise qualitative identification we have carried out initial extraction of the plasma in acetone; and, separately, have subjected the plasma samples to paper-electrophoresis.

Method

9 ml. of blood was taken into a clean glass syringe, oiled with silicone fluid ('M.S. 550', Hopkin & Williams). For single samples from a peripheral vein or artery, needle puncture was used; when serial samples were required from a central site, such as hepatic vein or pulmonary artery, the blood was taken via a no. 8 or 9 U.S.A. cardiac catheter, a fresh syringe being used for each specimen. The blood was at once discharged into 1 ml. of 3·2% sodium citrate in a polyethylene centrifuge tube, which was then stoppered with a silicone bung, inverted gently, and placed in iced water. The blood samples were spun down at 3000*g* for 40 minutes at 2°C, using a swing-out head. A platelet-count was done on the supernatant plasma, which was now virtually free from platelets. Separate counting on each sample was advisable, since we showed that contamination with only a few platelets could considerably influence the assay result. The plasma was separated using siliconed-glass pasteur pipettes, put in polyethylene tubes, and either assayed directly or stored frozen.

The fundal strip was set up in a bath of Tyrode's solution and the assay was made by bracketing the response of the plasma sample between known doses of serotonin-creatinine sulphate. Additional specificity was achieved by adding atropine sulphate (10^{-7}) and mepyramine maleate (2×10^{-7}) to the bath, and by showing that the response was virtually abolished by the addition of 2-bromo-lysergic acid diethylamide (10^{-6}). Using this technique we have been able to estimate the free plasma-serotonin in rapid serial samples withdrawn from a variety of sites in patients with carcinoid disease. The recovery of serotonin-creatinine sulphate, added to blood samples and taken through the same procedure, has been about 80%. Fig. 1 shows the fluctuations in the free plasma-serotonin in samples withdrawn from the right atrium of a patient with carcinoid disease, 1·3 mg. of serotonin-creatinine sulphate (dose expressed in terms of the base) being injected into an ankle vein at the time indicated.

Results

We found the peripheral venous level of free plasma-serotonin in four consecutive patients with established carcinoid disease and normal platelet-counts was between 20 and 60 ng. per ml. (expressed as the base).

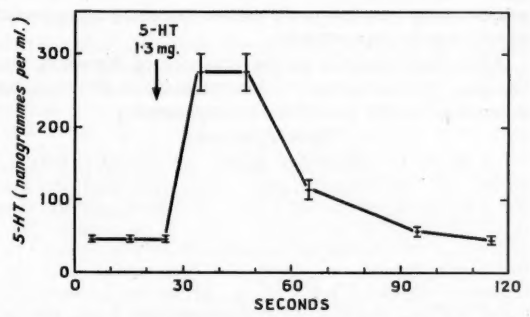


Fig. 1—Free plasma-serotonin levels in plasma taken from right atrium after injection of 1·3 mg. of serotonin into an ankle vein.

The horizontal bars indicate the bracket limits between which the value for each estimation lay.

These figures may be falsely high, and are, at least partly, raised by the breakdown of a few platelets with a high serotonin content while the blood sample is being taken. This view is supported by our findings in a fifth patient with carcinoid disease, who also had thrombocytopenia. In this man the peripheral venous free plasma-serotonin level was less than 10 ng. per ml. at a time when the platelet-count was only 10,000 per c.mm.

To identify the substance responsible for an increase in plasma activity, such as took place in one patient with carcinoid disease during flushing attacks (Peart et al. 1961), additional procedures—acetone extraction of the plasma, and paper-electrophoresis—were carried out:

In the biological assay of serotonin using the rat's uterus, initial extraction with acetone is usually done (Hardisty and Stacey 1955, Amin et al. 1954). For the accurate quantitative estimation of serotonin in plasma samples, we omitted this stage, partly for convenience and partly because, in our hands, the losses were variable. Plasma showing increased activity on assay of the neat samples was, however, taken through the initial extraction procedure described by these workers, approximately 70% of the activity remaining. This further

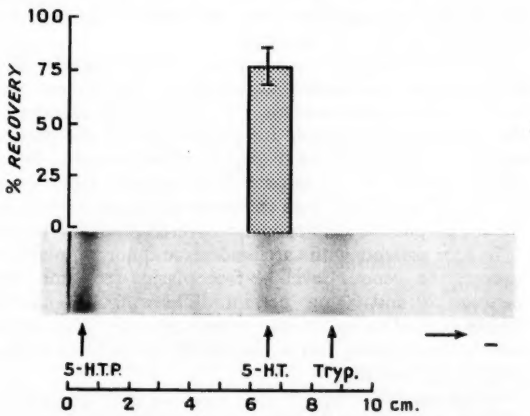


Fig. 2—Electrophoretic strip, developed in Ehrlich's solution, of a plasma sample containing added serotonin, 5-hydroxytryptophane (5-H.T.P.), and tryptamine hydrochloride. (Tryp.)

O=line of origin. Poorly shown in photograph, but present in all developed electrophoretic strips of plasma, is a pink zone lying between the 5-H.T.P. and serotonin bands. Upper part of diagram indicates the recovery of activity from eluates of an electrophoretic strip run in parallel with reference paper. Between 65 and 85% of the activity of plasma added to paper was recovered, and this was all found in the position corresponding to serotonin on reference paper.

supported the view that in the patient concerned the increased activity was due to serotonin.

Additional evidence of the presence of serotonin was obtained by subjecting the plasma samples showing the increased activity to paper-electrophoresis.

Electrophoresis

0·1 ml. of the platelet-free plasma was applied in 0·01 ml. portions to 3 MM Whatman paper 5 cm. wide, previously prepared by washing in distilled water. The line of application was dried in a current of cool air after each 0·01 ml. portion. With each run, a reference paper was prepared carrying an aliquot of the plasma sample, to which had been added serotonin-creatinine sulphate 1 mg. per ml., tryptamine hydrochloride 2 mg. per ml., and DL-5-hydroxytryptophane 2 mg. per ml. These quantities were sufficient to give definite colours when developed in Ehrlich's solution (Jepson 1955). Electrophoresis was carried out at room temperature in a horizontal tank at 10 V per cm. length and with a current of 10 mA, using pH 3·8 citrate buffer (0·035 *M* citric acid and 0·015 *M* sodium citrate). At the end of six hours the papers were removed and were dried in a stream of cool air. The reference paper was then developed in Ehrlich's solution, the serotonin appearing rapidly as a compact linear bluish-purple band between 6 and 7 cm. from the point of origin. The tryptamine and 5-hydroxytryptophane bands appeared slightly later than the serotonin, the 5-hydroxytryptophane remaining at or close to the line of application, the tryptamine migrating further towards the cathode than the serotonin (fig. 2). The plasma proteins appeared as a wide purple-pink band, between the 5-hydroxytryptophane and the serotonin.

After the reference paper had been developed, the paper carrying the plasma sample was cut into 1 cm.-wide transverse strips, which were then eluted with Tyrode's solution, and the eluates were assayed biologically as before. 65-85% of the initial activity of the plasma was recovered from the paper. In the case mentioned, the entire activity was found to lie in the position occupied by serotonin on the reference paper (fig. 2), no activity being recovered from elsewhere on the paper.

Summary

Free plasma-serotonin levels are an essential estimation in carcinoid disease, but they are difficult to measure, and the results published by different workers vary widely. The most sensitive method is biological assay using the fundal strip of the rat's stomach (Vane 1957). Under favourable circumstances this preparation will respond to 0·1 ng. (10^{-9} g.) of serotonin.

Vane's original method has been modified slightly. For more precise qualitative identification the plasma was initially extracted in acetone. To confirm the identity of the substance responsible for plasma activity the plasma samples were submitted to paper-electrophoresis. Serotonin appears as a compact bluish-purple band lying between 6 and 7 cm. from the point of origin; 65-85% of the initial plasma activity was recovered from the paper.

In four patients with carcinoidosis and normal platelet-counts, the venous level of free plasma-serotonin was between 20 and 60 ng. per ml. These figures may be falsely high, since a fifth patient with carcinoid disease and thromobocytopenia had a plasma-serotonin level of less than 10 ng. per ml.

We are grateful to Sandoz Ltd. for supplying serotonin-creatinine sulphate, and to Roche Products Ltd. for supplying DL-5-hydroxytryptophane and tryptamine hydrochloride.

REFERENCES

Amin, A. H., Crawford, T. B. B., Gaddum, J. H. (1954) *J. Physiol.* **126**, 596.
Goble, A. J., Hay, D. R., Sandler, M. (1955) *Lancet*, ii, 1016.
Hardisty, R. M., Stacey, R. S. (1955) *J. Physiol.* **130**, 711.
Jepson, J. B. (1955) *Lancet*, ii, 1009.
Magalini, S. I., Stefanini, M. (1956) *Proc. Soc. exp. Biol., N.Y.* **92**, 788.
Peart, W. S., Andrews, T. M., Robertson, J. I. S. (1961) *Lancet*, i, 577.
Pernow, B., Waldenström, J. (1957) *Amer. J. Med.* **23**, 16.
Sjoerdsma, A., Weissbach, H., Terry, L., Udenfriend, S. (1957) *ibid.* **23**, 5.
Vane, J. R. (1957) *Brit. J. Pharmacol.* **12**, 344.
Zucker, M. B., Borrelli, J. (1955) *J. appl. Physiol.* **7**, 425.

SENSITISATION OF BLOOD-VESSELS TO HYPERTENSIVE DAMAGE BY X-IRRADIATION

A. W. ASSCHER
M.B., B.Sc. Lond., M.R.C.P.
LECTURER IN MEDICINE

C. WILSON
M.A., D.M. Oxon., F.R.C.P.
PROFESSOR OF MEDICINE

SALLY G. ANSON
B.Sc. Southampton, M.Inst.Biol.
RESEARCH ASSISTANT

From the Medical Unit, The London Hospital, E.1

IN a previous paper Wilson et al. (1958) reported experimental observations on the relation of hypertension to structural renal damage after X-irradiation of the kidneys in rats. It was noted that when hypertension developed after *unilateral* renal irradiation, arterial necroses were more severe, and arose in vessels of larger calibre, in the irradiated than in the non-irradiated kidney. This observation suggested that X-irradiation had increased the susceptibility of the renal arteries to hypertensive damage. We here describe experiments by which this hypothesis was tested.

Wilson and Byrom (1941) showed that the rat mesentery was a common site for hypertensive arterial necroses; we therefore decided to study the effects of irradiation and hypertension separately and in combination in this vascular territory. A loop of mesentery was irradiated, and, at monthly intervals thereafter, hypertension was produced by renal-artery constriction. The incidence of vascular lesions in the irradiated loop was then compared with that in the remainder of the mesentery in hypertensive animals, and in control animals which were irradiated but were not submitted to renal-artery clipping.

Material and Methods

Fifty normotensive female rats of the Wistar strain, aged between 60 and 90 days, weighing between 160 and 220 g., and maintained on a stock diet and tap water, received 1200r irradiation of an exteriorised loop of mesentery, the rest of the animal being protected by 1·5 mm. lead shields. X rays were from a Victor therapy set working at 220 kV and 15 mA. The rays were filtered through 0·5 mm. of copper and 1 mm. of aluminium. The half-value layer was 1 mm. of copper. Irradiation was applied to the mesentery by means of a 5 × 3 cm. rectangular 'Perspex' applicator mounted on a baseplate and fixed to the main tube housing after the normal "master cone" had been removed. The focus-skin distance was 16 cm. The dose-rate at the applicator face was about 300r per minute, with back-scatter from the tissue. The irradiated loop of mesentery was marked with black silk stitches or silver clips for future recognition, and it was then returned to the abdominal cavity.

Renal-artery clipping was performed, after excising the opposite kidney, in groups of ten rats at monthly intervals for 4 months after mesenteric irradiation. These intervals were chosen in order to determine how quickly irradiation affected the response of the arteries to hypertension. The animals were killed a month after application of the clip to the renal artery, whether or not hypertension had developed, and the mesentery was examined and then fixed in formol-alcohol for histological study. Blood-pressure was measured by a modification of the tail plethysmographic technique (Byrom and Wilson 1938) under light ether anæsthesia. In these experiments the blood-pressure rose in a variable proportion of the animals, usually after 7 to 14 days. Hypertension had therefore been present for 2 to 3 weeks when the animals were killed. The control group comprised twelve animals which received 1200r X-irradiation to an exteriorised loop of mesen-

tery. The renal arteries were not clipped in this group, and the mesenteries were examined 2 months after irradiation.

In addition, the effect of varying the irradiation dose was studied on 6 groups of ten animals irradiated with doses ranging from 200 to 1200r. In this experiment the renal arteries were clipped a month after irradiation and the mesenteries were examined at monthly intervals thereafter for 3 months.

Results

Group 1 (a month after mesenteric irradiation and renal-artery clipping).—Five rats became hypertensive in this group, and their blood-pressure curves are shown in fig. 1. No macroscopic or microscopic vascular lesions were found in the mesenteries.

Group 2 (2 months after mesenteric irradiation and a month after the renal artery was clipped).—As shown in fig. 1 all the rats in this group became hypertensive. Eight showed gross lesions of the mesenteric vessels confined to the irradiated portion of the mesentery. The abnormal vessels appeared as thick cords (fig. 2), and nodules were palpable along their length (fig. 3). Histologically the cord-like thickening of the vessel walls was due to replacement of the medial and adventitial coats by inflammatory cell infiltration, chiefly with plasma-cells and young fibroblasts but also with many polymorphonuclear cells and eosinophils. Focal areas of fibrinoid necrosis were present in both intima and media. The endothelium of affected vessels was intact. In medium-sized arteries extensive intimal thickening with fibrinoid or fibrinohyaline material was often present (fig. 4). In such vessels the internal elastic lamina was greatly stretched and often fragmented. The arterioles and smaller arteries occasionally showed fibrinoid necroses (fig. 5). No vascular lesions were found in those parts of the mesentery which had not been irradiated nor in other organs examined (adrenal, myocardium, and gut).

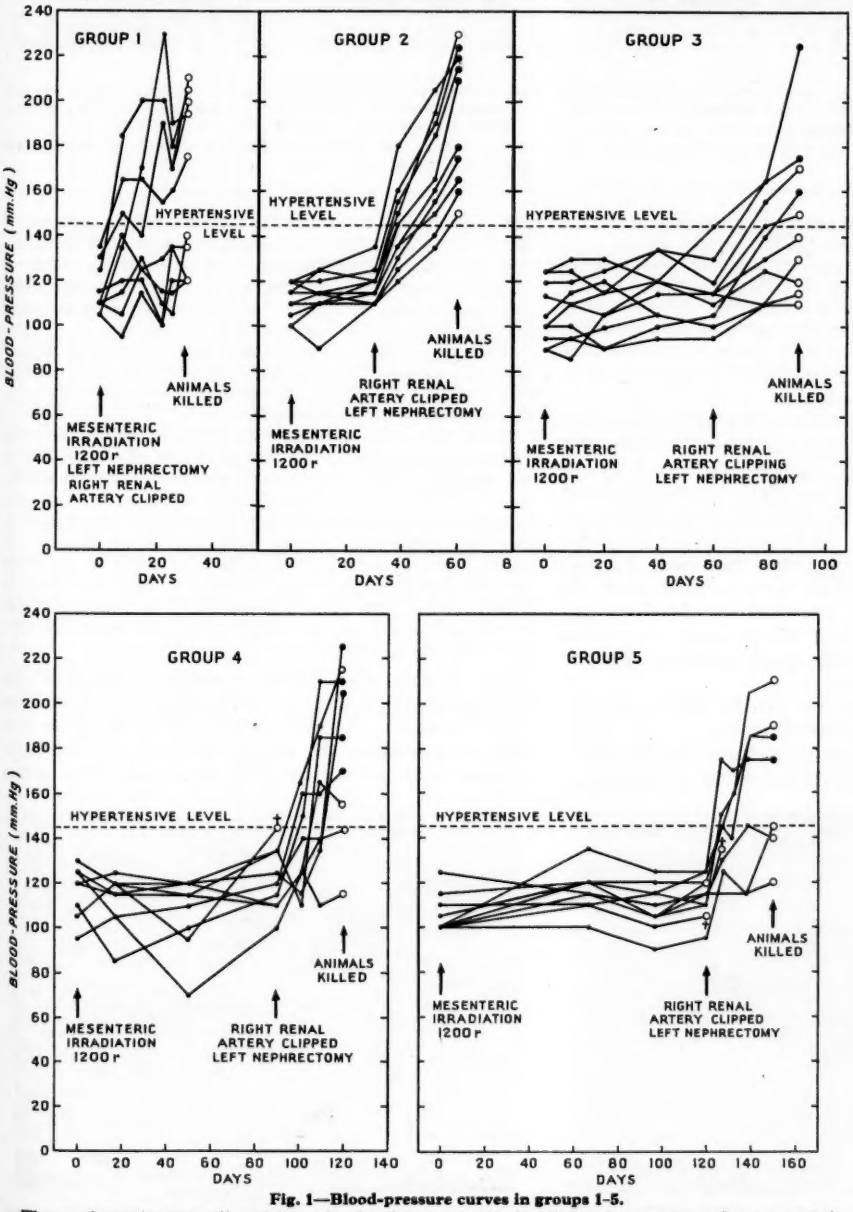


Fig. 1—Blood-pressure curves in groups 1–5.

The renal arteries were clipped immediately after mesenteric irradiation in group 1; after a month in group 2; after 2 months in group 3; after 3 months in group 4; and after 4 months in group 5.

O=rats with normal mesenteric vessels. ●=rats with arterial necrosis in the irradiated mesentery.

Groups 3, 4, and 5.—Similar vascular lesions were observed in the irradiated mesentery of hypertensive rats in the remaining groups, in which the interval after irradiation was 3, 4, and 5 months respectively (fig. 1). No lesions were observed in animals which failed to develop hypertension. Fig. 6 summarises the results in graphic form. It will be noted that sensitisation of the mesenteric vessels to the damaging effect of hypertension was not established until 2 months after 1200r irradiation, and continued for at least 5 months.

Controls.—In the control animals, no lesions resembling those described above were observed in either the irradiated or non-irradiated mesenteries. In one rat a group of mesenteric arteries showed chronic round-cell infiltration of the adventitia with some endothelial proliferation in one vessel. But no similar lesion was found in any other experimental animal in this investigation, and the relevance of these changes is doubtful.

Dose response.—The effect of irradiation dose on the sensitisation effect is shown in fig. 7. Doses less than 1000r did not

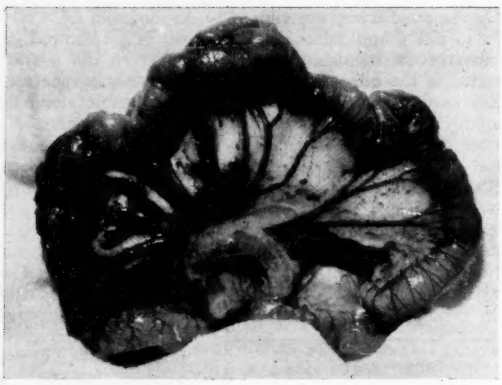


Fig. 2—Rat mesentery (in vivo) showing cord-like thickening of arteries in the irradiated part of the mesentery (on the left). The arteries in the non-irradiated mesentery (on the right) are normal. Hypertension of moderate severity (maximum 175 mm. Hg for 3 weeks).

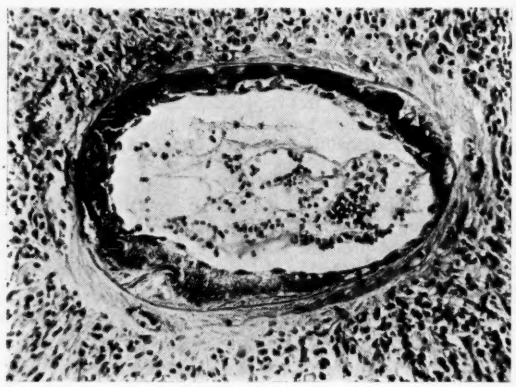


Fig. 4—Medium-sized mesenteric artery exposed to irradiation and 3 weeks hypertension (maximum 220 mm. Hg), showing subendothelial fibrinohyaline material. (H. & E. × 170.) The internal elastic lamina has lost its wrinkled appearance and is ruptured in places.

produce sensitisation even after an interval of 4 months. At the higher dosage levels (1000 and 1200r) arterial lesions were observed in the irradiated mesentery 2 months after irradiation. These were seen only in hypertensive rats, and animals showing no macroscopic lesions at 2 months did not develop them later. The observations were not continued beyond 4 months since with progressive rise in blood-pressure hypertensive lesions begin to appear in non-irradiated tissues at this time.

Discussion

The vascular lesions described above are identical with those observed in the mesentery when severe hypertension is produced by renal-artery clipping (Wilson and Byrom 1941). In the present study enough time had not elapsed for the blood-pressure to reach the high levels required to produce vascular lesions in the non-irradiated parts of the mesentery or in the other tissues examined (adrenal, myocardium, and gut). Moreover irradiation alone did not produce the lesions. We conclude, therefore, that 2 months after 1000 or 1200r X-irradiation, the arterial wall becomes more vulnerable to the damaging effects of increased intravascular pressure.

Damage to blood-vessels is a well-recognised effect of ionising radiations. Numerous studies of the histopathology of this form of vascular damage have appeared: Baerman and Linser (1904) in their study of X-irradiated human skin, considered that the most sensitive component of the vessel wall was the endothelium, which showed vacuolisation, swelling, and proliferation, sometimes to the extent of obliterating the vascular lumen, and at others forming a nidus for superimposed thrombus formation; other changes were fissuring and round-cell infiltration of the media.

Wolbach (1909) confirmed these observations and further noted destruction of the elastic lamina, increased thickness and vacuolisation of the medial smooth-muscle cells, and separation of these cells by collagenous fibrils.

Several observers have described fibrinoid arterial necroses in human uterus, and in the muscles of the rabbit and dog in the neighbourhood of radium implants (Lacassagne 1922, Letulle 1922, Dobravalskaia-Zavadskaia 1924). But the inadequate dosimetry of this early work makes it impossible to correlate histological damage with irradiation dosage. It seems, however, that high doses of ionising radiations can cause necrotic arterial lesions closely resembling those produced by hypertension. Thus Russell et al. (1949) described fibrinoid arterial necrosis in the arteries of the rabbit's brain 101 days after 2850r X-irradiation.

Our experiments provide no direct evidence of the mechanism of this increased susceptibility to hypertensive arterial necrosis. An obvious explanation would be that irradiation weakens the vessel wall—e.g., by structural damage to the endothelium or to the muscle-fibres of the

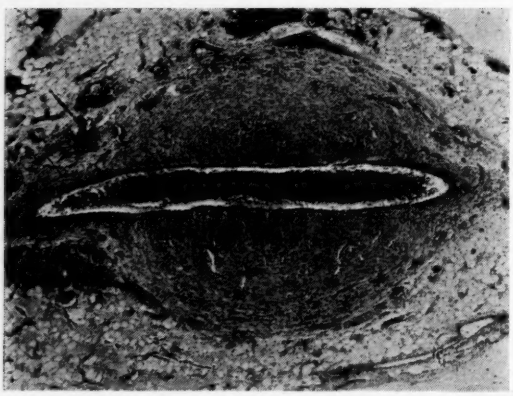


Fig. 3—Irradiated mesenteric artery showing nodule formation. Maximum blood-pressure 215 mm. Hg. (Hæmatoxylin & eosin. × 27.)

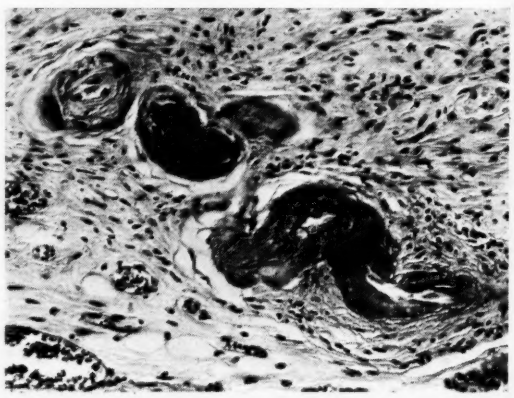


Fig. 5—Arterioles in irradiated mesentery after 3 weeks hypertension (maximum 220 mm. Hg), showing fibrinoid necrosis. (H. & E. × 190.)

media—and that such vessels more readily undergo mechanical disruption when the intravascular pressure rises. But we have not found any evidence of such endothelial or medial changes in irradiated vessels not exposed to hypertension at the time when the increased susceptibility develops.

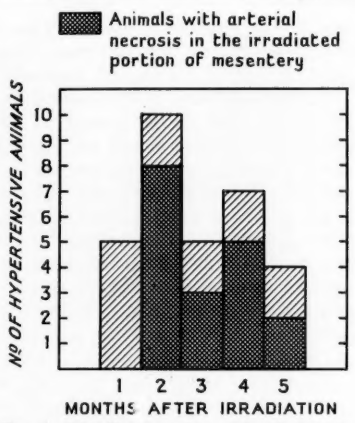


Fig. 6—Distribution of vascular lesions in the irradiated mesentery of hypertensive rats.

An alternative possibility is suggested by the work of Byrom (1954) who obtained unequivocal evidence that, in rats, severe hypertension led to focal arterial spasm in the brain and mesentery. His observations strongly suggest that this focal excessive vasoconstriction is a myogenic reaction to increased intravascular pressure, which may lead to arterial necrosis. It is possible, therefore, that irradiation of blood-vessels increases their susceptibility to hypertensive damage by exaggerating their myogenic response to variations in intravascular pressure—i.e., by reducing the threshold stimulus at which normal and excessive vasoconstriction occurs. It has been previously shown (Wilson et al. 1958) that, under certain experimental conditions, no obvious structural basis may be found for the hypertension which follows irradiation of the kidney. If, however, the myogenic reactivity of the renal-arterial system were sufficiently increased, physiological variations in the blood-pressure could lead to excessive vasoconstriction in these vessels. The resulting renal ischæmia might then give rise to hypertension in the same way as structural narrowing of the renal arteries. The sequence of events which we have observed after irradiation of the kidneys is consistent with this hypothesis, since the increased susceptibility of the arteries to a rise in intra-arterial pressure is observed 2 months after irradiation, the blood-pressure starts to rise after about 3–4 months, and arterial necroses develop when hypertension is established at a high level.

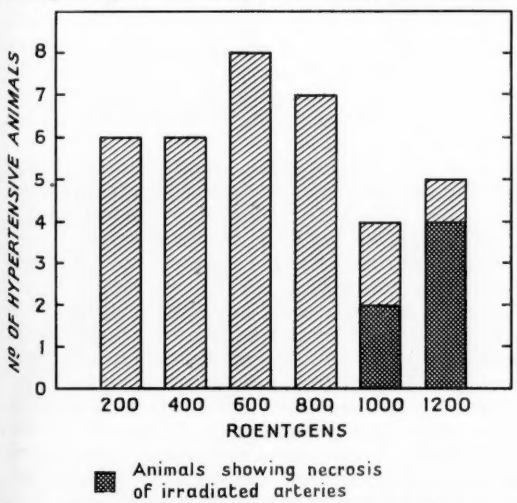


Fig. 7—Dose-response of hypertensive lesions in the irradiated mesenteric arteries of the rat.

The results of these experiments have a further implication which may be of clinical importance. Whatever the underlying mechanism, irradiation and raised intravascular pressure seem to be complementary in their damaging effects on the vessel wall. This may be relevant to the delayed tissue necrosis which occasionally follows therapeutic irradiation, and which is well known to be associated with arterial necrosis. If, as seems likely, the tissue necrosis is the result of vascular damage, we might expect it to arise with greater ease and frequency in hypertensive patients. We might also expect that those organs (kidney, pancreas, adrenal, intestine, and brain) in which hypertensive arterial necroses most commonly arise, would most often show late irradiation damage. These possibilities are being investigated.

Summary

It has previously been observed, in rats, that hypertensive vascular necrosis is more severe in an irradiated than in a non-irradiated kidney. From controlled experiments evidence has now been obtained that X-irradiation with doses of 1000 or 1200r increases the susceptibility of the mesenteric arteries to hypertensive vascular damage. The possible implication of these findings is discussed in relation to hypertension which follows irradiation of the kidneys.

We are grateful to Dr. J. M. Ledingham for his most helpful suggestions, and to Dr. M. Cohen for his help in irradiating the animals. We are indebted to Mr. J. King and Mr. R. Ruddick for the photographs.

REFERENCES

Baerman, G., Linser, P. (1904) *Münch. med. Wschr.* **51**, 996.
Byrom, F. B. (1954) *Lancet*, ii, 201.
— Wilson, C. (1938) *J. Physiol.* **93**, 301.
Dobravalskaia-Zavadskaia, N. A. (1924) *Lyon chir.* **21**, 397.
Lacassagne, A. (1922) *Pr. méd.* p. 323.
Letulle, M. (1922) *ibid.* p. 121.
Russell, D. S., Wilson, W. C., Tansley, K. (1949) *J. Neurol. Psychiat.* **12**, 187.
Wilson, C., Byrom, F. B. (1941) *Quart. J. Med.* **34**, 65.
— Ledingham, J. M., Cohen, M. (1958) *Lancet*, i, 9.
Wolbach, S. B. (1909) *J. med. Res.* **21**, 415.

INVETERATE DISLOCATION OF THE HIP

Historical Review and Case-report

F. WILLIAM SHEA
M.Ch. Orth. Lpool, F.R.C.S.
SENIOR REGISTRAR, THE GENERAL INFIRMARY, LEEDS

WITH the increase in serious motor accidents, traumatic dislocation of the hip has become a common injury but it is often overshadowed by other injuries, particularly those of the same limb. In spite of a general awareness of this pitfall, dislocations of the hip do sometimes remain undiagnosed, only to present later as a difficult problem for treatment—a problem that is rarely discussed and about which little has been written recently. This article reviews the available writings, and records a case in which reasonably good function was restored in the affected hip.

Historical Review

Manipulative Reduction

Astley Cooper (1826) stated: "I am of the opinion that eight weeks after the accident may be fixed as the period at which it would be imprudent to make the attempt at reduction." Volkmann (1893) found that in dogs, after experimental dislocations, the acetabulum filled with soft, easily removed connective tissue in fourteen days. This

tissue was firmly adherent after four weeks and became a hard fibrous mass by eight weeks. These results were confirmed by Miltner and Wan (1933), and they agree with the surgical findings of Harris (1894), Dollinger (1912), Buchanan (1920), and Miltner and Wan (1933). These authors do not specify a time-limit for attempted manipulative reduction, but their writings suggest that four weeks is the critical period, and that attempts made later may result in fractures, paralysis, and rupture of vessels.

Cauchoix and Ramadier (1949) accepted the possibility of manipulative reduction within the first four weeks, and described a patient whose dislocated hip was reduced after twenty days and who had a painless hip with 90° free flexion two years later. D'Aubigné and Ramadier (1959) believe that, while it may be possible, manipulative reduction should not be attempted if the dislocation has been present for more than a few days because of the risk of producing avascular necrosis of the femoral head.

Operative Treatment

The first report of operative treatment for unreduced dislocation is that of Delagarde (1866) who operated on one Robert Harford, aged 51, of Tiverton, Devon, in 1861. This patient had a dislocation of the hip associated with a double fracture of the femoral shaft. Four months later when the fractures were united, the femoral head and neck were excised with relief of persistent sciatic-nerve symptoms. The report concludes: " He died in the Summer of 1864 of pneumonia, having slept in the rain one Saturday night, instead of going home as a sober man would."

The first operative reduction was achieved by Polaillon (1883) in a patient who had had an obturator dislocation for six weeks. This patient died of gas gangrene within a few days of operation.

Dollinger (1912) reported 17 patients treated by arthrotomy. Of these, the head of the femur was resected in 4, an osteotomy was done in 1, and 12 dislocations were reduced. Of these 12, 6 became infected and required resection of the head while the remaining 6 progressed to " permanent recovery ". Duration of follow-up is mentioned in only 3, and the times were twenty-one months, three-and-a-half years, and five years.

Buchanan (1920) collected and analysed the case-reports of 50 patients treated by operative reduction. The duration of the dislocation was less than four months in 30, and in 46 was less than one year. Results were said to be good in 80% of the reports analysed.

Fig. 1—Inveterate dislocation of left hip showing well-developed false acetabulum and no significant bony injury.

Miltner and Wan (1933) reported 16 of their own patients in Peking. An initial period of skeletal traction was employed to bring down the head to the level of the acetabulum. The Smith-Petersen incision was used and reduction was achieved in all. The results are described as excellent in 8 patients, good in 1, fair in 4, and poor in 2. Movements in the 8 " excellent " patients are stated as not less than 75% of the normal range. Radiographs showed osteoarthritic changes in 80% of all the patients, though few had symptoms. Times of follow-up are mentioned in only 5 of the 8 " excellent " patients and are six months, seven years, two months, three years, and seven months.

Campbell (1936), describing dislocations of the hip-joint with accompanying fracture of the acetabulum, mentions 14 patients, treated late either by open reduction or by arthroplasty, only to say the results were poor.

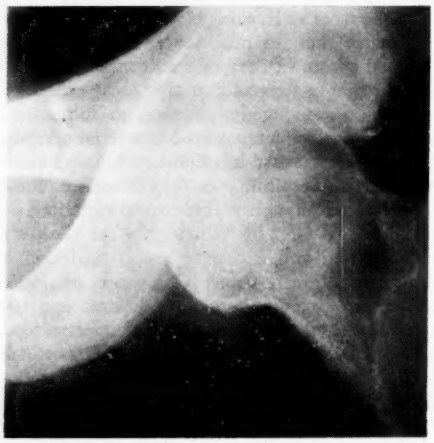


Fig. 2—Immediate postoperative radiograph. Reduction is not concentric.

Cauchoix and Ramadier (1949) described the treatment of 7 patients with inveterate dislocation of the hip. In 2 of 3 patients in whom it was done, open reduction produced clinically normal hips in a short-term follow-up of six months. Similar good early results were obtained in 2 patients in whom acrylic prostheses were used to replace damaged and deformed femoral heads. Resection of the femoral head with replacement of the neck into the acetabulum resulted in painful unstable hips in both cases in which it was carried out.

Stewart and Milford (1954) report 12 patients with fracture-dislocations operated on one month or more after injury. Reduction of the dislocation was achieved in all the patients, but there was only 1 good result.

Mikhail (1956) reported the successful open reduction of an inferior dislocation of the hip one year after injury but there is no record of the late result. Hamada (1957) described the treatment of 3 old anterior dislocations. In these patients the abduction/external-rotation deformities were corrected by osteotomy at the base of the neck.

D'Aubigné and Ramadier (1959) analysed the results in 43 patients treated in eight years. Almost all of these dislocations were complicated by fractures of the femoral head, femoral neck or shaft, or the acetabulum. The late results of open reduction in 6 patients were all poor. In 16 patients, treated by acrylic-replacement arthroplasty,

Fig. 3—Radiograph of hip six weeks after open reduction. Reduction has become concentric.

results were initially good but deteriorated with time. 2 of the 4 patients in whom cup arthroplasty was done and who were followed up obtained good function. The best results were obtained by arthrodesis. Of 10 patients in whom late review was carried out, 9 were classed as good or very good.

Case-report

A man, aged 24, was involved in a motor-cycle accident. On admission he was found to have a closed fracture of the lower third of the shafts of the left tibia and fibula. The fracture was manipulated under general anæsthesia and immobilised in a full-leg plaster-of-paris cast. The tibial fracture was clinically united after thirteen weeks, but very little callus was visible on the radiograph. Because of this immobilisation was continued for seventeen weeks.

Twenty weeks after the accident, during physiotherapy, the patient fell and complained for the first time of pain in his left hip. He was found to have an inveterate posterior dislocation of the hip, without complicating fracture (fig. 1). After skeletal traction for one week, open reduction of the dislocated hip was carried out twenty-one weeks after the original accident.

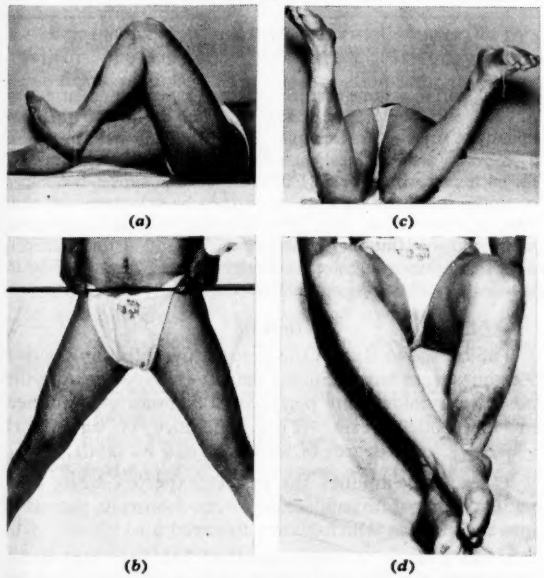


Fig. 4—Movements of hip one year after operative reduction: (*a*) flexion; (*b*) abduction; (*c*) internal rotation; (*d*) external rotation.

Operation.—Under general anæsthesia the hip-joint was approached by the method described by McFarland and Osborne (1954). The acetabulum was full of firm fibrous tissue and a fibrous capsule bound the head of the femur to its false acetabulum. This capsule and the contents of the acetabulum were excised. The limits of normal articular cartilage could not be defined so that an irregular surface remained after excision. There were no visible changes in the head of the femur. Reduction was easily accomplished by traction alone. The reduction was stable in full abduction increased in degree by an adductor tenotomy.

In the postoperative period, skeletal traction in wide abduction was maintained for six weeks. The radiograph immediately after operation (fig. 2) showed that reduction was not truly concentric, probably because of the irregularity of the acetabulum. Whilst under treatment by traction, the patient carried out daily active exercises with the object of "smoothing off" this irregularity. A radiograph at the end of six weeks (fig. 3) showed that the femoral head had sunk into its socket with resulting concentric reduction. Mobilisation was then started with rapid progress to full weightbearing, and the patient returned to his work as a draughtsman three weeks after discharge from hospital. The movements of the hip gradually improved and his activities returned to normal.

Fig. 5—Radiograph of left hip one year after open reduction. There is well-developed periarticular ossification.

Seventeen months after the original accident, and one year after the open reduction of the inveterate dislocation, the patient had no pain and was able to continue his usual work and leisure activities without any disability. He walked without any limp. There was no deformity of the hip and no significant shortening of the leg. The range of movements is shown in fig. 4. Fig. 5 is a radiograph of the left hip-joint at this time.

Conclusions

Good functional result was obtained by open reduction of a twenty-week-old dislocation of the hip with no associated fracture.

Previous reports of some successful results support the conviction that operative reduction is the treatment for inveterate dislocation of the hip when there is no fracture of the acetabulum or of the head and neck of the femur. Operative reduction is less likely to be possible or successful where such a fracture coexists; and in such cases arthrodesis seems to be the treatment of choice.

It is a pleasure to thank Mr. A. B. Pain and Mr. J. M. P. Clark for their help and encouragement.

References overleaf

EFFECT OF PARATHYROIDECTOMY ON THE INCIDENCE OF RENAL CALCULI

MARY G. McGEOWN
M.D., Ph.D. Belf.

MEDICAL UROLOGIST, DEPARTMENT OF MEDICINE, THE QUEEN'S UNIVERSITY OF BELFAST, AND BELFAST CITY HOSPITAL

DURING the past decade hyperparathyroidism has been recognised as a fairly common disease, especially among patients with renal calculi. The true prevalence of hyperparathyroidism among patients with urolithiasis is unknown, but Cope (1942) suggested that it was between 10 and 15%. Fetter and McCuskey (1960), however, found only 6 cases among 172 patients who had undergone operation for stone disease.

Since February, 1955, I have seen 68 cases of hyperparathyroidism among 405 patients attending a renal-stone clinic, excluding those whose calculi were composed of cystine or uric acid. In 59 of these patients the hyperparathyroidism was confirmed on exploration of the neck. In the other 9 the parathyroid glands appeared normal at operation, but biochemical and clinical remission took place and has persisted for two to five years. This represents a prevalence of 17% of patients with calcareous stones, but this figure is too low because there is a waiting-list for operation; 10 patients have had exploratory operations with negative findings, but still have hypercalcæmia for which no cause can be found. If these were included, the prevalence would be about 22%; but even this figure is almost certainly too low because the serum-calcium characteristically fluctuates in hyperparathyroidism (McGeown and Morrison 1959), and some patients may have had episodes of hypercalcæmia which have been missed. On the other hand, though all the patients attending the stone clinic were investigated, they were to some extent selected cases because patients with recurrent stones are more likely to be referred there. Though these figures do not represent the true prevalence of hyperparathyroidism among patients with renal stones, they do show that it is a fairly common cause of stone.

The work involved in the diagnosis of hyperparathyroidism is considerable as the serum-calcium must be determined four or more times in each patient over a long period. It has been asked whether all this work is justified. These patients sometimes have rapidly recurring stones and general ill-health; but, in some, stones are formed only at long intervals and the general health does not appear to suffer. Their renal function would be expected to deteriorate gradually because of the hypercalcæmia; but this usually does not take place for a long time, probably because the hypercalcæmia is intermittent.

Is anything achieved by parathyroidectomy apart from improvement in the serum-calcium? The patients often remark on a general increase in well-being and appetite, even if they had not previously been aware of ill-health, but this cannot be measured objectively. The stone history of these patients can be studied objectively in an attempt to decide whether stone formation has been reduced by parathyroidectomy.

Methods

56 of the patients who have undergone parathyroidectomy have been kept under observation for from one to five years. In these patients the number of stones formed before and after parathyroidectomy was known and could be compared.

The duration of the disease was measured from the year in which the first stone was diagnosed, either by X-ray or by the passage of a stone to the time of operation. The initial stone was not counted, but, if bilateral stones were present when the patient was first seen, 1 stone was counted for the first year. This method of counting eliminated patients in whom hyperparathyroidism was diagnosed after the first stone. The stone history of each patient was set out in tabular form, each year before and each year after operation being treated separately. It was then possible to count the number of stones that had formed in all the patients in each preparathyroidectomy and postparathyroidectomy year, and the total number of patients observed in each year, and thus to arrive at the total number of stones observed in the total number of patient-years (omitting the presenting stone for each patient). If the patient had numerous small stones and it was impossible to decide whether a new stone had been formed after parathyroidectomy, the case was counted as a recurrence. Any increase in size of an existing stone was also counted as a recurrence. Thus the figures given for postoperative recurrences were weighted against showing any benefit from parathyroidectomy.

Because the stone history of each patient was known in detail, another approach was to use each patient as his own control, and to assume that the expected rate of stone formation in each postoperative year was the same as that in the preoperative years—for example, if the patient had produced 5 stones in eleven years, the expected rate of stone formation for each year would be 5/11 or 0·45. A total expected number of stones in all the patients could then be calculated for each year of observation after parathyroidectomy, and compared with the actual number of stones formed by all the patients. Again the presenting stone was not counted, but the year in which it occurred was considered to be year 1.

TABLE I—COMPARISON OF PREPARATHYROIDECTOMY AND POSTPARATHYROIDECTOMY HISTORY IN 56 PATIENTS

—	Preparathyroidectomy	Postparathyroidectomy	Total
Patient-years	401	158	559
Stones:			
Observed ..	99	8	107
Expected ..	76·8	30·2	107

(The expected numbers are proportional to the patient-years.)
$\chi^2 = 22{\cdot}72$ (1 degree of freedom), $P < 0{\cdot}001$.

Results

Table I shows that in the preparathyroidectomy period 99 stones were formed in 401 patient-years, whereas in the postparathyroidectomy period only 8 stones were formed in 158 patient-years. This difference is significant; $\chi^2 = 22{\cdot}72$ (on 1 degree of freedom), and $P < 0{\cdot}001$.

Table II exemplifies the results expected when each patient's preparathyroidectomy stone history is projected into the years in which he was followed up.

A had 2 stones in seven years and had been kept under observation for five years after parathyroidectomy, and his expected rate of stone formation would be 0·28 in each of the

MR. SHEA: REFERENCES

Buchanan, J. J. (1920) *Surg. Gynec. Obstet.* **31**, 462.
Campbell, W. C. (1936) *J. Bone Jt Surg.* **18**, 842.
Cauchoix, J., Ramadier, J.-O. (1949) *Rev. Orthopéd.* **35**, 548.
Cooper, A. (1826) A Treatise on Dislocations and on Fractures of the Joints. London.
D'Aubigné, R. M., Ramadier, J.-O. (1959) Traumatismes Anciens; p. 85.
Delagarde, P. C. (1866) *St. Bart's Hosp. Rep.* **2**, 183.
Dollinger, J. (1912) *Ann. Surg.* **55**, 177.
Hamada, G. (1957) *J. Bone Jt Surg.* **39B**, 471.
Harris, M. L. (1894) *Ann. Surg.* **20**, 319.
McFarland, B. L., Osborne, G. V. (1954) *J. Bone Jt Surg.* **36B**, 364.
Mikhail, I. K. (1956) *ibid.* **38B**, 899.
Miltner, L. J., Wan, F. E. (1933) *Surg. Gynec. Obstet.* **56**, 84.
Polaillon, M. (1883) *Bull. Soc. Chir. Paris*, **9**, 107.
Stewart, M. J., Milford, L. W. (1954) *J. Bone Jt Surg.* **36A**, 315.
Volkmann, R. (1893) *Arch. Klin. Chir.* **37**, 373.

TABLE II—EXPECTED HISTORY OF PATIENTS IF PREPARATHYROIDECTOMY HISTORY WAS PROJECTED INTO POSTPARATHYROIDECTOMY YEARS (EXAMPLE)

Patient	Preparathyroidectomy history*	Years after parathyroidectomy				
		1	2	3	4	5
A	2/7	0·28	0·28	0·28	0·28	0·28
B	5/18	0·27	0·27	0·27	0·27	0·27
C	4/2	2·00	2·00	2·00	2·00	2·00
D	2/5	0·40	0·40	0·40	0·40	..
E	2/5	0·50	0·50	..	..	..
Remainder†	..	..	..	..	..	..
Total ..	..	18·97	18·97	12·59	11·39	8·91

* Number of stones/number of years.
† Histories calculated and included in total, but not shown in body of table.

five years. In patients D and E, who had been kept under observation for four and two years respectively, their expected rate applied to four years and two years respectively. The total observed and expected stones are shown in table III. The difference is significant; $\chi^2=55{\cdot}92$ (on 5 degrees of freedom), and $P<0{\cdot}001$.

Discussion

When a large group of patients, such as the one here, is studied, they are found to form stones at very different rates, and this probably affects the results obtained when all the patients are aggregated as in table I. The comparison of preparathyroidectomy and postparathyroidectomy history is not completely valid unless all patients form stones at the same rate, which they obviously do not. There is no such objection to the use of each patient's preparathyroidectomy history as the control for the post-

TABLE III—COMPARISON OF EXPECTED AND OBSERVED STONE FORMATION AFTER PARATHYROIDECTOMY

Stones	Years after parathyroidectomy				
	1	2	3	4	5
Total observed	3·0	2·0	2·0	1·0	..
Total expected	18·97	18·97	12·59	11·39	8·91

$\chi^2=55{\cdot}92$ (5 degrees of freedom), $P<0{\cdot}001$.

parathyroidectomy years, and the histories of all the patients can then be added.

Both methods of treatment of the stone history of these patients who have undergone parathyroidectomy show a significant reduction in stone formation after this operation. Though the imperfections of the statistical treatment of this material are recognised, I feel that the figures justify the policy of investigating for hyperparathyroidism all patients who have renal stones.

Summary

The effect of parathyroidectomy on the formation of renal calculi has been investigated by comparing the postoperative histories of hyperparathyroid patients with the forecasts made by two statistical methods.

Both methods show that stone formation is significantly reduced after parathyroidectomy.

Because the prevalence of renal calculi in hyperparathyroid patients is at least 22%, all patients with renal calculi should be investigated for hyperparathyroidism.

I am grateful to Mr. Ernest Morrison, who carried out the parathyroid exploration on most of these patients; to the many surgeons who have generously referred their patients to me; and to Dr. S. J. Kilpatrick for advice about the statistical treatment.

REFERENCES

Cope, O. (1942) *J. Mo. med. Ass.* **39**, 273.
Fetter, T. R., McCuskey, B. M. (1960) *J. Urol.* **84**, 213.
McGeown, M. G., Morrison, E. (1959) *Post Grad. med. J.* **35**, 330.

INDIAN CHILDHOOD CIRRHOSIS

AMARJIT SINGH
M.D. Punjab, M.R.C.P.
PROFESSOR OF MEDICINE

S. S. JOLLY
M.D. Punjab
ASSISTANT PROFESSOR OF MEDICINE

LEELA R. KUMAR
M.R.C.P.E.
READER, PÆDIATRIC DEPARTMENT

MEDICAL COLLEGE, PATIALA, INDIA

CIRRHOSIS of the liver in adults is one of the commoner chronic diseases; but cirrhosis in children is uncommon, particularly in the temperate regions. In the tropics and subtropics, cirrhosis in children is somewhat commoner, but it is still less often found than the adult form of the disease. There appear to be only two regions from which childhood cirrhosis has often been reported—Jamaica and the subcontinent of India. The veno-occlusive disease of Jamaica is now well known, but Indian childhood cirrhosis, which is a distinct entity, is not recognised as such outside India.

The Indian childhood cirrhosis was first described by Sen (1887) in Calcutta. It was recognised as a common and widespread disease, responsible for hundreds of deaths yearly in Calcutta alone (Pearse 1910). The clinical features of the disease are well described by the Indian Council of Medical Research (I.C.M.R.) (1955):

" Infantile cirrhosis of the liver is a disease peculiar to India affecting infants and young children, with a tendency to run in families. It is characterised in the early stages by enlargement of the liver which is felt to be hard and usually also of the spleen, with ascites and jaundice superimposed at the later stages. Its onset is insidious with vague symptomatology, course variable, but generally rather slow and termination usually fatal. Its etiology is unknown."

The disease is almost confined to children between 1 and 3 years of age, and is decidedly commoner in the male. Though estimates of the familial incidence vary considerably, there is a tendency for the disease to run in families.

For clarity of description, many workers divide the clinical course into three allegedly well-defined stages—early, intermediate, and late. In practice these stages are not sharply demarcated, one stage merging imperceptibly into the next. In the early stages the child becomes irritable, is off-colour, and does not play. Diarrhœa, episodes of low-grade fever, flatulence, peevishness, and inability to thrive are common complaints. The liver is just palpable and feels firm with a rather sharp margin. The spleen also may be enlarged. In the intermediate stages the clinical features become more definite, rendering the diagnosis comparatively easy. The child looks very ill, is irritable, and may be frankly jaundiced. The liver is always palpable, having a characteristic " leafy " edge. The spleen is always enlarged, owing to the development of portal hypertension. Œdema of the ankles, some puffiness of the face, and ascites may appear. In the terminal stages the child has deep icterus. The abdomen becomes protuberant (figs. 1 and 2).

Methods and Material

The material for this study consisted of 114 children taken at random from the pædiatric and medical wards of a 500-bed teaching hospital at Patiala (Punjab).

Cases of infantile cirrhosis of known cause, such as con-

Fig. 1—Boy, aged 2, showing hepatomegaly, splenomegaly, tense ascites, and œdema of the legs.

Fig. 2—Bania Aggarwal child, aged 1½, showing hepatosplenomegaly, subacute form.

genital syphilis, infective hepatitis, Wilson's disease, rhesus incompatibility, galactosæmia, and other inborn errors of metabolism, were not included. A complete hæmogram, routine urinalysis and stool examination, and liver-function tests were done on each patient. Evidence of hæmolytic disease was sought in each case by the osmotic-fragility test, Coombs test, and Rh-grouping of the mother and child. Serological tests for syphilis were also made both in the mother and in the child. In the earlier phase of this work the urine chromatograms were also studied for excretion of any abnormal amino-acids, but, as chromatography did not yield any significant results, it was later abandoned. A percutaneous biopsy of the liver was performed with a Vim-Silverman needle.

Findings

Age and Sex

Most of the patients were between 1 and 3 years old, but the series included all ages from 8 months to 7 years. 11 patients were less than 1 year old and 9 were over 3. There were only 8 girls in the series, indicating the preponderance of the disease in boys. This observation agrees with the findings of other workers (Srivastava and Aikat 1954, Mukherji 1952, Chaudhauri 1944).

Racial and Religious Factors

This report covers a geographical area which is predominantly inhabited by Sikhs in the villages, yet there were only 33 Sikh children in this series. Of the remaining 81 patients, most (56) came from a particular sect of Hindus—the Bania Aggarwal group (table I).

This community of Hindus has been strictly vegetarian for generations, living on a simple and barely adequate diet lacking in animal proteins. Moreover, their marriages are usually confined to their own group. The genetic importance of this is obvious.

Family History

More than 1 sibling in the family was affected in 48 cases (42%), again emphasising the importance of genetic factors.

TABLE I—EFFECT OF HEREDITARY FACTORS

Group	No. of cases	% of total	% with family history
Bania Aggarwal ..	56	71·5	86
Other Hindus	25		26
Sikhs	33	28·5	15
Total	114	..	..

Clinical Features

The clinical features, laboratory data, and the histological findings of the series are summarised in fig. 3. Most of the cases could be clinically divided into 3 groups —fulminant, acute, and subacute.

In the fulminant cases, the illness progresses rapidly, and the child usually dies from hepatic failure within a month of the onset. 23 cases belonged to this group. The clinical features resembled those of infective hepatitis—hepatomegaly, deep icterus, ascites, and semiconsciousness. Histologically, there were no distinctive features in this group except that the necrosis of liver-cells is more widespread and eosinophil clumping was more in evidence than in other groups.

In the acute form of the disease the average duration of illness was 3 months. There were 27 cases of this type in the series. The clinical features were similar to those in the fulminant variety except in their intensity.

The subacute form of the illness was found in slightly older children, the average age being 2·5 years, compared with 1·3 in the fulminant group. The preponderance of this form in a particular Hindu sect was striking, because 55 cases out of a total of 64 in this group belonged to the Bania Aggarwal community. Similarly, a history of the

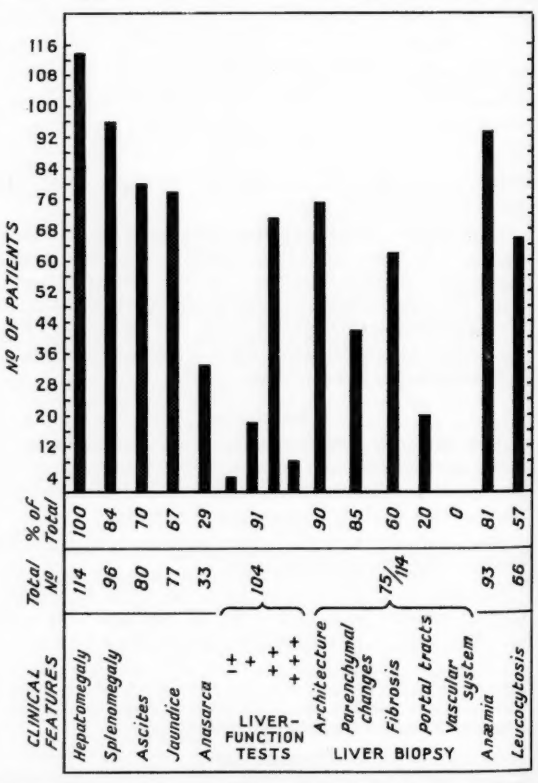


Fig. 3—Physical signs and laboratory data in 114 cases of Indian childhood cirrhosis.

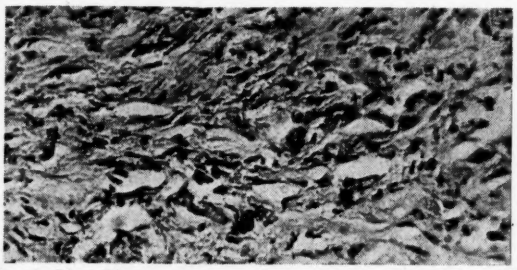


Fig. 4—Liver-biopsy specimen (hæmatoxylin and eosin; ×400) showing pericellular fibrosis and complete loss of hepatic architecture.

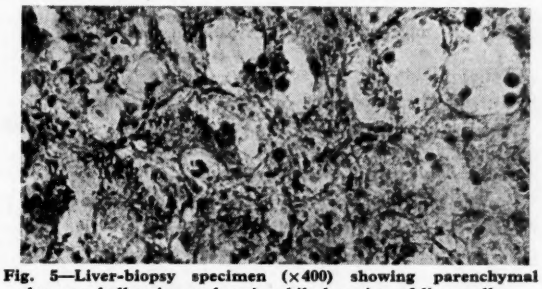


Fig. 5—Liver-biopsy specimen (×400) showing parenchymal changes—ballooning and eosinophil-clumping of liver-cells.

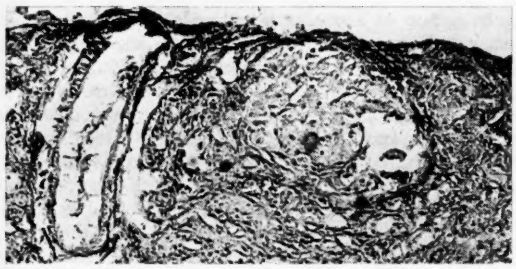


Fig. 6—Liver-biopsy specimen (van Gieson; ×160) showing pericellular fibrosis.

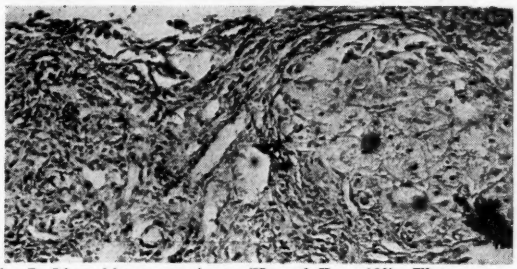


Fig. 7—Liver-biopsy specimen (H. and E.; ×160). There are no occlusive changes in hepatic veins

disease in other siblings was found in 86% of this group (table I). In the earlier stages the clinical features were confined to a hepatosplenomegaly. Later, symptoms of mild hepatocellular failure supervened. The prognosis was almost always grave, most patients passing to an advanced stage of liver-failure; but 4 recovered. These children remained healthy over a 3-year follow-up. The differences between the various types of the disease are shown in table II.

Histology

Histological data are scanty because few necropsies are permitted. In this series 85 liver biopsies were attempted in 75 patients; 3 children had serial biopsies so that the evolution of the condition could be studied.

The basic change appeared to be diffuse cell necrosis and replacement fibrosis. In the earlier stages there was patchy but widespread degeneration and necrosis of liver parenchyma. The liver-cells showed ballooning; hydropic change; disappearance of nuclei; and considerable variations in size, shape, and staining character of cells with loss of basophilia of cytoplasm. Such parenchymal changes with loss of hepatic architecture were found in all cases. The most conspicuous parenchymal change, seen in 83% of cases, was the degeneration of liver-cells into granular and smudged eosinophilic masses. Together with these necrotic changes, there was a change in the reticulin pattern, apparently brought about by swelling of cells. Later, there was condensation of reticulin fibrils in and around the portal tracts with formation of pseudolobules. The cirrhosis was typically portal. Eventually, the normal hepatic architecture was completely disorganised, and everywhere broad or narrow bands of fibrous tissue were seen surrounding small or large islands of degenerating parenchymatous cells. The pericellular fibrosis was quite typical and was present in 60% of cases (fig. 4–7). The connective-tissue septa were infiltrated with various types of cells in 20% of cases. There was also a varying degree of regeneration of liver-cells with the formation of regenerating nodules. The vascular tissues, particularly the smaller hepatic veins, were carefully scrutinised but no occlusive changes were found (fig. 7).

Discussion

Cirrhosis of the liver in infants and children is rare and has been seldom reported from countries outside India.

Craig et al. (1955) in Boston could collect only 98 cases over a 30-year period from 1924 to 1953. Similarly Ruggieri et al. (1957) found only 27 cases in the records of the Mayo Clinics from 1924 to 1954. In Great Britain only sporadic cases of cirrhosis associated with rare metabolic diseases have been published and no well-documented series are available (Baber 1956). Even in south-east Asian countries, such as Ceylon, Burma, and Indonesia, this type of childhood cirrhosis is extremely rare and is more often found in Indian immigrants than in the local population. On the other hand, this disease is one of the commonest pædiatric conditions in India, and as many as 3 or 4 cases are seen daily in the outpatient departments of children's hospitals in certain provinces (Mukherji 1952, Misra 1951).

Obviously Indian childhood cirrhosis is a disease in its

TABLE II—DIFFERENCES BETWEEN THREE FORMS OF INDIAN CHILDHOOD CIRRHOSIS

Type	No. of cases	Average age (yr.)	Sex ratio (M/F)	Average duration of illness (mos.)	Racial factors	Family history	Clinical picture	Histological appearances
Fulminant	23	1·3	20/1	1 or less	Hindu 11 Sikh 12	3%	Fulminant hepatocellular failure	Eosinophil clumping; inclusions and necrosis
Acute	27	1·6	25/2	1–3	Hindu 15 Sikh 12	15%	Mild hepatocellular failure	Less definite changes
Subacute	64	2·5	61/3	More than 3	Hindu 55 Sikh 9	75%	Subacute hepatosplenomegaly	Architectural disturbances and classical cirrhosis

TABLE III—COMPARISON OF VARIOUS TYPES OF "CHILDHOOD CIRRHOSIS"

Disease	Age	Sex	Other siblings affected	Socio-economic factors	Onset	Course	Hepato-megaly	Spleno-megaly	Ascites	Jaun-dice	Liver-function tests	Biopsy	Cause
Posthepatic cirrhosis	Any age from neo-natal period	Equally distributed	−	Commoner in poor sections	Subacute	Progressively downhill	+	±	+	+	++	Typical necrosis	Infective hepatitis
Veno-occlusive disease	1–6 yr.	„	+	„	Acute	Downhill—may recover	++	±	+	±	++	Occlusion of veins	Toxic bush-teas
Metabolic cirrhosis	Late childhood	Predominantly male	+	No effect	Chronic	Slowly downhill	+	±	±	±	+	Atypical features	Inborn errors of metabolism
Kwashiorkor	6 months onwards	Equally distributed	−	Very poor	„	Recovery possible	+	−	±	−	+	Fatty liver	Protein malnutrition
Indian childhood cirrhosis	1–3 yr.	Predominantly male	++	Not common in poor—usually in middle class	All types	Progressively downhill	+++	++	++	++	++	Typical histological appearances	Genetic and malnutritional

own right, met with only in the Indian subcontinent. In Western countries, cirrhosis follows an altogether different pattern. It is very rare, and the affected children are much older. The common causes of cirrhosis of liver in infants and children are: infective hepatitis (Ruggieri et al. 1957); rhesus incompatibility (Braid and Ebbs 1937); Wilson's disease (Uzman and Hood 1952); infections such as kala-azar, syphilis, malaria, and chronic intestinal infestations (Moon 1929); biliary obstruction (Hsia et al. 1954); glycogen-storage disease (Bridge and Holt 1945); Fanconi's syndrome (Bon and Bickel 1953); and transfusional siderosis (Ellis et al. 1953).

Another important variety of childhood cirrhosis, found in Jamaica, is caused by veno-occlusive disease of the liver (Bras et al. 1954, Stuart and Bras 1957). Many workers have been tempted to compare the two diseases (Jelliffe et al. 1957). Toxic effects of local herbal remedies is suggested as a possible cause. In both conditions, the children from the lowest economic group are not affected and inadequate diet is believed to play a part. Some workers have, moreover, found obliterative lesions of the smaller hepatic veins in the Indian cirrhosis (Radhakrishna Rao 1935, Jelliffe et al. 1957). Both the diseases show a familial incidence. In spite of having many features in common the two diseases are almost certainly distinct clinical entities with many basic differences (table III).

Veno-occlusive disease shows no definite age distribution as does Indian childhood cirrhosis. Veno-occlusive disease may affect much older children, and even adults are not always spared. It commonly has an acute onset with hepatomegaly and œdema, which thus resembles that of the Budd-Chiari syndrome of which veno-occlusive disease may be considered an intrahepatic form. Jaundice appears much later than in Indian childhood cirrhosis; and even after a careful search by many workers (Achar and Chacko 1954, I.C.M.R. 1955, Singh et al. 1959) and by us in the present series, no occlusion of smaller hepatic veins—the basic lesion in veno-occlusive disease—was found. There is close resemblance between the two diseases in the terminal stages, but every organ in the body has only a limited number of sterotyped responses to various noxious influences of which an almost limitless number can affect the liver. Thus, widely differing factors may lead to a similar result.

Heredity

Almost all workers admit that heredity plays a part in the causation of this disease. A positive family history of the disease has been found in 7–50% of all cases, and was present in 46% of the cases in our series. The disease most often involves siblings of the patient; but sometimes collaterals, and even parents, have been attacked. Mukherji (1952) recorded instances of infantile cirrhosis in binovular twins. Further, the predilection of the disease for certain castes—e.g., the involvement of a particular Hindu group in a predominantly Sikh-inhabited area—clearly indicates the importance of genetic inheritance. What is inherited still remains uncertain. Prabhu (1940) suggested that a constitutional weakness of the liver was inherited which made it more vulnerable to such factors as malnutrition and infection. Probably a biological inferiority is inherited which is unmasked by some other influence. Similarly, the exact mode of inheritance is still not precisely known. The inheritance is obviously not by a direct dominant gene, because children who suffer from the disease do not usually, when adult, transmit the disease directly. Transmission must therefore be through symptomless carriers of recessive genes with low and irregular penetrance. No definite pedigrees have been reported to which mendelian laws can be applied. Since most workers have found the prevalence is greatest among male children (93% of the present series) sex-linked genes may be responsible (Merchant 1952).

Nutritional Factors

The part played by malnutrition in adult Laennec's cirrhosis is well recognised (Glynn and Himsworth 1944). This factor, however, is not the only one because the diet of families having Indian childhood cirrhosis is no different from that of others; moreover, this entity is rare in the extremely poor and usually affects the middle classes. This form of childhood cirrhosis has never been reported from other countries in which malnutrition is as severe and as common as in India. In our study, more than 80% of the children were breast-fed; and, on the whole, the nutrition of the mother as well as that of the child was found deficient, particularly in animal proteins. Malnutrition, however—particularly shortage of proteins—produces the fatty liver of kwashiorkor rather than the liver of childhood cirrhosis. Conceivably malnutrition may be a contributory factor, acting in conjunction with heredity but it cannot be the sole cause.

Infective Factors

Narayanamurthi and Trimurthi (1939) first suggested that the disease may be caused by a hepatotoxic virus, analogous to that of infective hepatitis. This was later emphasised by Kutumbiah (1951). Ruggieri et al. (1957) found the cirrhosis was postnecrotic in 26 out of 27 cases in children. Stokes et al. (1951) described a case where a mother, who later was proved to be carrying an icterogenic virus, gave birth to a child that had jaundice at 4 months and fibrosis of liver at 18 months. Dible et al. (1954) drew attention to the possibility of intrauterine hepatitis as a cause of juvenile cirrhosis. The I.C.M.R. subcommittee also studied the liver-biopsy specimen from a case of severe infectious hepatitis at full term in a woman who gave birth to a stillborn fœtus. A liver-biopsy specimen from the

mother showed pronounced cellular necrosis. The liver of the fœtus showed diffuse necrosis, multinucleated liver-cells, and evidence of active hæmopoiesis. Infective hepatitis is widespread, and yet childhood cirrhosis has been reported rarely as a complication.

The histological changes with the liver in childhood cirrhosis do not resemble those of infective hepatitis, but some changes in the liver parenchyma—namely, eosinophil hyaline bodies—suggest a virus infection (Srivastava and Aikat 1954). So far, however, no infective agent has been isolated, and attempts to transmit the disease to laboratory animals have been unsuccessful. Mukherji et al. (1954) reported the isolation of a filter-passing agent in the stools of children with infantile cirrhosis which, when injected into 8-week-old albino rats, produced in 6–8 weeks a patchy necrosis of liver-cells and also an increase in peripheral connective tissue with round-cell infiltration. We have tried a similar experiment with a filtrate from the stools of patients with childhood cirrhosis, but we could not produce any hepatic changes in the newly born rats to whom the filtrate was given.

Toxic Factors

The recent discovery that veno-occlusive disease is probably caused by toxins derived from the bush-teas has revived interest in the toxic hypothesis of childhood cirrhosis. Jelliffe et al. (1957), drawing support from experimental evidence and veterinary medicine, pointed out that certain plant toxins may sometimes act on liver-cells and/or on hepatic veins. No such toxins, however, have yet been found by any worker in India, and the evidence in favour of the toxic hypothesis is slender.

Rhesus Incompatibility

Hawksley and Lightwood (1954) drew attention to cirrhosis in children with erythroblastosis fœtalis; but this is not a common cause of cirrhosis, and Gerrard (1952) could not find a single case in which cirrhosis followed erythroblastosis fœtalis. In India, erythroblastosis fœtalis is rare. The present investigation, where the results of various tests done on almost all the children and their parents clearly exclude any hæmolytic factor, proves that these agents have no importance as causal factors in Indian childhood cirrhosis.

Inborn Errors of Metabolism

That rare inborn errors of metabolism—galactosæmia, Fanconi's syndrome, Wilson's disease, mucoviscidosis, glycogen-storage disease, &c.—may be associated with cirrhosis is well known. None of these diseases is ever responsible for Indian childhood cirrhosis; and no case in this series had any clinical or laboratory evidence of these rare metabolic disorders.

Summary

114 patients with childhood cirrhosis were studied in Punjab (India). The disease is predominantly encountered in boys aged 1–3 years. It is characterised by progressive hepatic failure with hepatomegaly, splenomegaly, jaundice, and ascites. Prognosis is uniformly unfavourable, most of patients dying of the disease within a year of its onset.

Three clinical forms of the disease—fulminant, acute, and subacute—are distinguished. Needle biopsy of the liver revealed a distinctive histological picture with necrosis and eosinophil clumping of the liver-cells, fibrosis of portal type involving small groups of cells, and complete loss of hepatic architecture. The veins of small and medium size were completely normal.

The disease apparently arises by genetic inheritance coupled with malnutrition.

Indian childhood cirrhosis is a distinct clinical entity almost confined to the subcontinent of India and is unlike any other type of cirrhosis found elsewhere.

We are very much indebted to Dr. M. Balasubrahmanyan and Dr. S. D. Khanna for the histopathological studies; to Dr. J. S. Gill and Dr. S. P. Gupta for the clinical notes of a few cases; and to Mr. G. S. Sekhon for the microphotography.

REFERENCES

Achar, S. T., Chacko, R. (1954) *Indian J. med. Sci.* **8**, 442.
Baber, M. D. (1956) *Arch. Dis. Childh.* **31**, 335.
Bon, H. S., Bickel, H. (1953) *Acta pædiat., Stockh.* **42**, 90.
Braid, F., Ebbs, J. H. (1937) *Arch. Dis. Childh.* **12**, 389.
Bras, G., Jelliffe, D. B., Stuart, K. L. (1954) *Arch. Path. (Lab. Med.)* **57**, 285.
Bridge, E. M., Holt, L. E. (1945) *J. Pediat.* **27**, 299.
Chaudhauri, K. C. (1944) *Indian J. Pediat.* **11**, 61.
Craig, J. M., Gellis, S. S., Hsia, D. Y. Y. (1955) *Amer. J. Dis. Child.* **90**, 299.
Dible, J. H., Hunt, W. E., Pugh, V. W., Steingold, L., Wood, J. H. F. (1954) *J. Path. Bact.* **67**, 195.
Ellis, J. T., Smith, C. H., Schulman, I. (1953) *Amer. J. Path.* **29**, 578.
Gerrard, I. W. (1952) *Brit. med. J.* i, 1385.
Glynn, L. E., Himsworth, H. P. (1944) *J. Path. Bact.* **56**, 297.
Hawksley, J. C., Lightwood, R. (1954) *Quart. J. Med.* **29**, 155.
Hsia, D. Y. Y., Hsia, H. H., Green, S., Kay, M., Gellis, S. S. (1954). *Amer. J. Dis. Child.* **88**, 458.
Indian Council of Medical Research (I.C.M.R.) (1955) *Indian J. med. Res.* **43**, 723.
Jelliffe, D. E., Bras, G., Mukherjee, K. L. (1957) *Arch. Dis. Childh.* **32**, 369.
Kutumbiah, P. (1951) Proceedings of the Scientific Advisory Board, I.C.M.R.; p. 129.
Merchant, A. (1952) *Indian J. Child. Hlth*, **1**, 53, 115.
Misra, S. S. (1951) *Acta. med. scand.* **140**, suppl. 259, p. 181.
Moon, V. H. (1929) *Amer. J. med. Sci.* **177**, 681.
Mukherji, S. K. (1952) *J. Indian med. Ass.* **22**, 6.
— Rangam, C. M., Pohowalla, J. N., De, H. N. (1954) *Trans. Indian Ass. Path.*; p. 42.
Narayanamurthi, K., Trimurthi, T. S. (1939) *Indian J. Pediat.* **6**, 85.
Pearse, T. F. (1910) *Indian med. Gaz.* **45**, 107.
Prabhu, M. B. (1940) *Indian J. Pediat.* **7**, 121.
Radhakrishna Rao, M. V. (1935) *Indian J. med. Res.* **23**, 57.
Ruggieri, B. A., Baggenstoss, A. H., Logan, G. B. (1957) *Amer. J. Dis. Child.* **94**, 64.
Sen, B. C. (1887) *Indian med. Gaz.* **22**, 338.
Singh, A., Jolly, S. S., Subrahmanyan, B. (1959) *Brit. med. J.* i, 278.
Srivastava, J. R., Aikat, B. K. (1954) *Indian J. med. Sci.* **8**, 446.
Stuart, K. L., Bras, G. (1957) *Quart. J. Med.* **26**, 291.
Stokes, J., Woltman, I. J., Blanchard, M. C., Farquhar, J. D. (1951) *Amer. J. Dis. Child.* **82**, 213.
Uzman, L. L., Hood, B. (1952) *Amer. J. med. Sci.* **223**, 392.

THE ADMINISTRATION OF OXYGEN

J. A. C. BALL
M.D., B.Sc. Belf.
SENIOR REGISTRAR,
DEPARTMENT OF THERAPEUTICS AND PHARMACOLOGY,
THE QUEEN'S UNIVERSITY OF BELFAST

MANY methods have been devised for giving oxygen, and their efficiency has been estimated by measuring the oxygen content of samples of alveolar air before and during oxygen administration (Poulton and Adams 1936, Christie 1938, Card et al. 1940, Christensen 1946). To make these measurements, oxygen administration has to be stopped while the patient produces an alveolar air sample by a maximum expiration. Analysis of these samples shows that their oxygen content depends on the precise level of ventilation at the moment before sampling, and also, to a lesser extent, on the patient's cooperation in producing maximum expiration on demand. The composition of alveolar air varies even during one exhalation, especially in subjects with pulmonary disease (Lilly 1950, Comroe and Fowler 1951). Because cooperation by the patient is essential, most estimates of the efficiency of oxygen administration have been made on healthy subjects.

It seemed that useful information might be obtained if the common methods of oxygen administration were re-assessed, using arterial oxygen saturation as a measure of efficiency. With this method, less cooperation is demanded from the patient; and, by taking many samples of arterial blood, variations in oxygen saturation caused by small variations in ventilation can be assessed.

Method

Three methods of oxygen administration in common use—the oxygen tent (Oxygenaire Ltd.), the B.L.B.-type mask (J. G. Franklin & Sons Ltd.), and the Tudor Edwards catheter carrier (spectacles) (British Oxygen Gases Ltd.)—were examined. At first a fourth method, using the polymask (British Oxygen Gases Ltd.), was tested. In use, however, this mask was found uncomfortable, and difficult to fit accurately to the face. It slipped from the correct position so readily and tube-kinking occurred so often that it was abandoned as too unreliable for common use. An improved form of this mask has recently become available, but has not been tested. Great care was taken to ensure that the tent was well sealed and that the mask and spectacles were properly applied.

Oxygen was given to ten patients with emphysema. They had received no food or therapy for at least the preceding twelve hours. A sampling-needle remained in the brachial artery throughout each trial. None of the patients developed signs of carbon-dioxide narcosis during oxygen administration; indeed, experience in this hospital indicates that carbon-dioxide narcosis is rare, occurring in less than 5% of patients with respiratory disease who are given oxygen.

Samples of arterial blood were taken while the patient breathed air, twenty to thirty minutes after the needle had been inserted. Oxygen was then given to each patient by each method successively in random order, and further samples withdrawn. Samples were also obtained while breathing air between each administration. The oxygen saturation of these was found to be not more than 3% greater than that of the initial sample, provided half an hour elapsed between each test. On each occasion, three samples were withdrawn at two-minute intervals, and the values obtained agreed within 0·5%, indicating that a steady state had been reached.

Estimations of blood-oxygen saturation were made, as soon as possible after the samples had been taken, using a photoelectric colorimeter with a cuvette (Roddie et al. 1957), previously calibrated against a Van Slyke manometric apparatus.

Results

The results are shown in the table.

Tent samples were taken after flushing the tent with oxygen at 12 litres per minute for twenty minutes, and then reducing the flow to 8 litres per minute. Mask and spectacle samples were taken with oxygen flowing at a rate of 4 litres per minute. Provided the mask was fitted properly, this was found to be sufficient to ensure that the reservoir bag remained partly inflated at the end of each inspiration. If the patient's resting ventilation is high, a greater flow may be necessary to flush out the dead space of the mask. Oxygen to the mask was fed through a Woulfe's bottle as this was found to be more comfortable for the patient. The presence of water at the bottom of the reservoir bag after a few hours' use of the oxygen mask does not mean that the inspired gas is adequately humidified. Though no measure of the saturation of the inspired gas was made, several patients complained of dryness of the mouth and throat when oxygen flow to the mask was direct and not through the Woulfe's bottle. Oxygen to the spectacles was passed through a nebuliser which ensured supersaturation of the inspired gas with water.

ARTERIAL OXYGEN SATURATION BEFORE AND AFTER OXYGEN

Patient	Initial sample breathing air	Oxygen tent (8 litres per minute flow)	Oxygen mask (4 litres per minute flow)	Oxygen spectacles (4 litres per minute flow)
1	74·5%	90·4%	95·7%	90·2%
2	73·8%	88·7%	97·0%	95·6%
3	77·7%	95·5%	98·4%	96·6%
4	61·9%	95·5%	97·2%	96·7%
5	77·2%	90·7%	95·7%	91·1%
6	84·0%	94·4%	95·5%	93·3%
7	90·8%	93·3%	95·2%	95·6%
8	83·3%	91·3%	96·7%	93·7%
9	70·4%	90·5%	95·5%	90·7%
10	84·3%	89·4%	94·1%	92·7%

Each value is the mean of three separate estimations made on each of three samples withdrawn at 2-minute intervals.

The results were analysed using the paired *t*-test. The mask produced significantly higher arterial oxygen saturation than the tent ($P < 0.001$), or the spectacles ($0.01 > P > 0.001$), and the spectacles were just significantly better than the tent ($0.05 > P > 0.02$). Thus the mask is the most efficient method of giving oxygen. The arterial oxygen saturation obtained when oxygen is given by spectacles at a flow-rate of 4 litres per minute is significantly higher than when a tent is used with a flow of 8 litres per minute. All methods raised arterial oxygen saturation to almost normal levels; and it is doubtful whether the slightly greater increase in oxygen saturation of arterial blood obtained with a mask—though statistically significant—is of much importance from the patient's point of view.

Discussion

Oxygen is usually administered by nurses, and patients receiving oxygen are not, as a rule, in a fit state to cooperate intelligently in their treatment. It is of paramount importance, therefore, that the method of oxygen administration used should be one which is simple to set up and requires the minimum of cooperation from the patient.

Though the mask is the most efficient method of oxygen administration, its use requires continuous skilled attention. A slight leak between the facepiece and the patient's face, a sticky reservoir bag, or an improperly inserted oxygen inlet-tube, decrease its efficiency greatly. The mask is difficult to fit to a patient with a large nose or with a receding chin. False teeth must be kept in place. Errors in the positioning of the mask can, to some extent, be corrected by increasing the rate of oxygen flow; but this is wasteful, and even at flow of 6–8 litres per minute, small leaks around the mask seriously reduce its efficiency.

The oxygen tent has been subjected to much criticism. Many patients find the heat intolerable, even in modern refrigerated tents. Many dyspnœic patients object to the feeling of being closed in. Feeding, bed-changing, physiotherapy, and general nursing are difficult. Carbon-dioxide accumulation within the tent is not usually of much practical importance because—though it would inevitably occur were the patient left undisturbed in a well-sealed tent for several hours—the tent is voided fairly often to room air for nursing purposes. In this series, the carbon-dioxide content of tent-air never exceeded 0·7% at oxygen content of from 60 to 80%.

Tudor Edwards spectacles were found to be simple in use; the rubber catheters were at least 2 in. long, and were liberally coated with local anæsthetic cream before insertion. Spraying beforehand with local anæsthetic greatly relieved the discomfort of insertion. Supersaturation of the oxygen with water is of great importance, and, when this was done with a nebuliser, no patient complained of discomfort with the spectacles. Measurements indicated that it made little difference whether the patient's mouth was open or closed; and, provided that the patient did not actually remove the spectacles, arterial oxygen saturation remained high whatever their position. Carbon-dioxide accumulation cannot, of course, occur with spectacles, and slow withdrawal of oxygen is easy.

Summary

The efficiency of oxygen administration using an oxygen tent, a mask, and Tudor Edwards spectacles was examined, using the level of arterial oxygen saturation as a criterion.

The mask was found to be significantly better than the tent or the Tudor Edwards spectacles; but the spectacles were found to raise arterial oxygen saturation a little more than an oxygen tent. Reasons for preferring Tudor Edwards spectacles as a general method of oxygen administration are given.

My thanks are due to Mr. J. M. Collins for his technical assistance and to Dr. F. D. Honneyman who helped to calibrate the colorimeter.

REFERENCES

Card, W. I., Smith, J. F., Griffiths, W. J., McSwiney, B. A., Savage, B. (1940) *Lancet*, i, 398.
Christensen, E. N., Urry, A. G., Cullen, S. C. (1946) *Anesthesiology*, **7**, 399.
Christie, R. V. (1938) *Lancet*, ii, 876.
Comroe, J. H., Fowler, W. S. (1951) *Amer. J. Med.* **10**, 408.
Lilly, J. C. (1950) *Amer. J. Physiol.* **161**, 342.
Poulton, E. P., Adams, T. W. (1936) *Brit. med. J.* i, 567.
Roddie, I. C., Shepherd, J. T., Whelan, R. F. (1957) *J. clin. Path.* **10**, 115.

Preliminary Communication

THE INTERACTION OF BRETYLIUM WITH PRESSOR AGENTS

MANY reports stress the frequency with which hypertensive patients who initially respond to bretylium become tolerant to the drug after a variable period of treatment, even though the dose is increased to many times its original level, and Boura et al.[1] suggested that this tolerance might be due to increased sensitivity to adrenaline and noradrenaline.

We are investigating the interaction of pressor agents with bretylium in man, and, in view of the recent discussion of the mechanism of tolerance, present our findings so far. Experimental subjects were normal volunteers and patients under treatment for hypertension.

RESULTS

Fig. 1 illustrates enhancement of the pressor effect of noradrenaline after a single dose of bretylium given to four normal subjects. The dose of bretylium used was the smallest to produce evidence of sympathetic blockade as shown by postural hypotension or characteristic changes in the blood-pressure response to Valsalva's manœuvre—i.e., a marked fall in mean pressure and pulse

1. Boura, A. L. A., Green, A. F., McCoubrey, A., Laurence, D. R., Moulton, R., Rosenheim, M. L. *Lancet*, 1959, ii, 17.

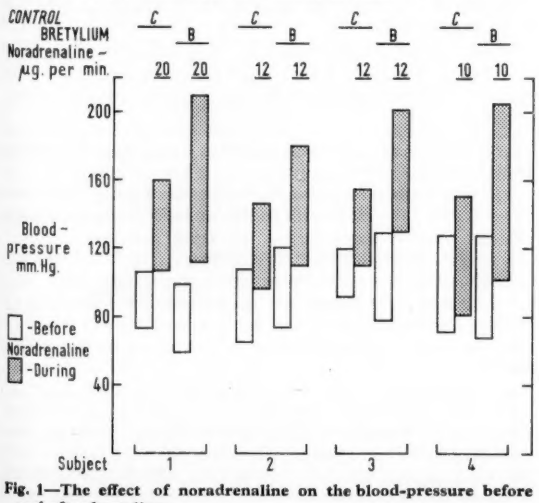


Fig. 1—The effect of noradrenaline on the blood-pressure before and after bretylium.

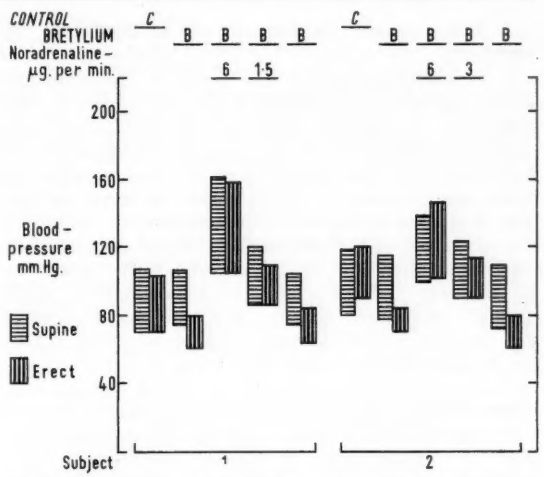


Fig. 2—The effect of noradrenaline on the postural hypotension produced by bretylium.

pressure, absence of a secondary rise in blood-pressure, and absence of an overshoot. Similar experiments showed that the response to adrenaline is also enhanced. The pressor effect of hypertensin, on the other hand, is not affected by bretylium.

Bretylium has little vasodilator effect in the supine subject,[2] and presumably produces hypotension by blocking the change in vasomotor tone which is the normal response to standing. Our next experiments were designed to study the effect of a continuous steady infusion of noradrenaline on the orthostatic hypotension produced by bretylium. Fig. 2 shows, in two subjects, that such an infusion will temporarily abolish the fall in blood-pressure when the subject is upright.

In an attempt to throw light on the mechanism of this, the effect of noradrenaline infusions on the response to Valsalva's manœuvre was studied after the latter had been modified by bretylium. We have found that with an intravenous dose of 8 μg. noradrenaline per minute, the shape of the blood-pressure record changes from that characteristic of sympathetic blockade to a square-wave response similar to that found in cases of heart-failure.[3] At lower doses of noradrenaline, such as 2 μg. per minute, which will still prevent diastolic hypotension on standing, an intermediate type of response is seen.

If circulating noradrenaline is the antagonist to bretylium in the tolerant state, adrenolytic drugs such as phentolamine might be expected to abolish tolerance and restore postural hypotension. Nine hypertensive patients who were tolerant to large doses of bretylium have been given phentolamine in a dose of 5 mg. intravenously. All of them had a fall in supine blood-pressure which varied from 30/18 to 95/42 mm. Hg, while their postural fall in blood-pressure, which before phentolamine was slight or absent, varied from 20/10 to 80/40 mm. Hg. In some of these patients continuous blood-pressure records were taken during Valsalva's manœuvre. In every case there was a considerable change after phentolamine, with an exaggeration of the features characteristic of sympathetic blockade.

SUMMARY AND COMMENT

1. Adrenaline and noradrenaline are potentiated by bretylium in man as they are in animals.

2. Taylor, S. H., Donald, K. W. *ibid.* 1960, ii, 389.
3. Sharpey-Schafer, E. P. *Brit. med. J.* 1955, i, 693.

2. The response to hypertensin is unaffected by bretylium.

3. Steady infusions of low doses of noradrenaline abolish the postural hypotensive effect of bretylium. We cannot yet say whether this is due to restoration of conduction in sympathetic pathways—a possibility which we had in mind at the beginning of this investigation but which has received no support from the results so far. The fact that a square-wave response to Valsalva's manœuvre occurs with the higher doses of noradrenaline suggests an alternative mechanism—i.e., that it might act by preventing the changes in cardiac output which normally accompany changes in posture and so remove the necessity for compensatory vasoconstriction. This possibility is being further investigated.

Applied Pharmacology Research Unit,
Medical Unit,
University College Hospital,
Medical School,
London, W.C.1

D. R. LAURENCE
M.D. Lond., M.R.C.P.
R. E. NAGLE
M.B. Cantab.

New Inventions

HÆMATOLOGICAL PIPETTES AND A TEAT DEVICE FOR RAPID DELIVERY OF SMALL MEASURED QUANTITIES

IN the estimation of blood-coagulation factors by Quick's test, thrombotest, or the thromboplastin-generation test, it is essential that small accurately measured quantities of reagents are delivered rapidly into small test-tubes containing the various reaction mixtures.

Two sources of error commonly arise with pipettes of the usual design, which often have too many calibration marks on the stem, or a tip which is too wide and difficult to insert into the opening of a narrow test-tube. Moreover with the conventional rubber teats fitted to such pipettes there is difficulty in retaining small measured quantities at the required calibration mark; this often happens when the pipette has to be moved before its contents are expelled.

Pipettes and a teat device, as shown in the figure, have solved these problems. With only one calibration mark these

pipettes are made to deliver quantities from 0·10 to 0·50 ml. The long tip ensures easy entry into a small test-tube. The teat device comprises a one-hole rubber stopper with a specially designed *moulded* rubber cap stretched over one end. The conventional latex rubber vaccine-bottle cap is not suitable because of its flexibility, and because it has a thick rubber ring which prevents it being held steadily. The two parts of this teat device are easily separated for cleaning.

In use, the upper end of the pipette is inserted into the uncovered end of the teat device. The pipette is held between three fingers and the thumb of one hand, leaving the index finger free to exert light pressure or to remain relaxed on top of the rubber cap. By these manipulations, fluid is drawn into the pipette and held easily at the calibration mark. Rapid delivery is effected by quickly pressing the top of the cap with the index finger. In the thromboplastin-generation test there is no difficulty in simultaneously controlling a second pipette in the other hand.

I am grateful to Dr. Robert Ollerenshaw, department of medical illustration, Manchester Royal Infirmary, for the photograph. The pipettes have been made to my design by Messrs. H. G. Elliott, E-Mil Works, Pontypridd, Glam. The teat-device components are obtainable through Griffin & George, Ltd., Alperton, Wembley, Middlesex.

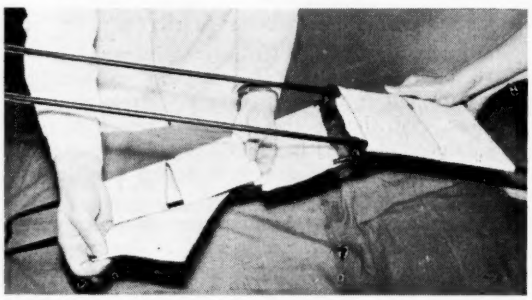
Department of Clinical Pathology,
Manchester Royal Infirmary

H. LEMPERT
M.D., M.SC. Manc., A.R.I.C.

A SLING FOR THE THOMAS SPLINT

IN lower-limb fractures, the Thomas splint is extensively used to maintain reduction and to control alignment. The splinted limb rests on cloth slings; these are usually of terry towelling or domette bandage, fastened with large paper-clips or with safety-pins. Their disadvantages are: (*a*) a tendency for the slings themselves to stretch or to slide, thus letting the splinted limb sag; (*b*) the material may fray, or be torn by the safety-pins; (*c*) the paper-clips tend to slip; (*d*) the life of the material is short, particularly terry towelling; (*e*) great care is necessary to keep the splinted limb neat and tidy for any length of time.

Strips of minute nylon hooks have recently been produced which will grip strongly a similar strip of brushed nylon pile



when pressed on to it. This simple, neat method has wide practical applications, not least in the Thomas splint. It is already used in the cuff of a sphygmomanometer.

The material 'Velcro' is obtainable by the yard: the package includes a length of each component. The largest contains 36 yd. of each, rolled separately. The strips are $1^1/_4$ in. wide. Lengths of strong, non-stretch white webbing 5 in. wide, measuring 24 in., 21 in., and 18 in. are obtained, and three parallel 6-in. strips of velcro are firmly stitched to the webbing $^1/_2$ in. from its end, the hooklet strips at one end, and the brushed nylon pile strips at the opposite end of the webbing, and on the reverse side.

Once adherent the slings will resist a very large force before they separate.

The slings are wrapped round the bars of the Thomas splint (see figure). They have been used in the orthopædic unit of the Western General Hospital, Edinburgh, and have the following advantages:

1. Ease of application; these slings can be partially overlapped, without loss of efficiency.

2. Readjustments are unnecessary unless the sling slips down to a narrower part of the Thomas splint; this can happen only to the distal sling on the splint.

3. Nothing else is needed to fix the sling.

4. The slings will not fray since the webbing is seamed.

5. The sling is long-lasting as it can be washed without losing its adhesive properties.

6. The sling lies neatly on the splint and there is no superfluous material.

My thanks are due to Mr. J. H. S. Scott for his encouragement and permission to use these slings on his patients; and to Selectus, Ltd. (Biddulph, Stoke-on-Trent, Staffordshire), the manufacturers, for supplies of 'Velcro'.

Orthopædic Unit,
Western General Hospital,
Edinburgh

R. S. PHILLIPS
M.B. Edin., F.R.C.S.E.
Registrar

Reviews of Books

The Management of Fractures and Soft Tissue Injuries

Committee on Trauma of the American College of Surgeons. Philadelphia and London: W. B. Saunders. 1960. Pp. 1372. 35*s*. (In two paper-bound volumes: *Fractures* 12*s*.; *Soft Tissue Injuries* 16*s*.)

TEN years ago the really good textbooks on fractures were few. Scarcely any book dealt, in a general way, with other aspects of traumatic surgery: and most doctors in the United States and this country read the works of the same few authors. Today, several first-rate books on accident surgery and orthopædics are published on both sides of the Atlantic every year, and each of them must have some special distinction to attract favourable attention, even in its country of origin.

This volume can claim such distinction: in part, because it is issued under the ægis of an internationally acknowledged authority; in part, because it is attractively produced and very reasonably priced; but principally because it treats its subject in an unusually direct and practical way. The reader will look in vain for a lengthy dissertation on the causes of non-union, or the nature of the biochemical imbalance in burns. But he will find, if he is confronted by a case of developing cerebral compression, or a penetrating eye injury, precise instructions about what to do. The very features which limit the value of this book for the undergraduate, or those preparing for predominantly theoretical examinations, make it ideal as a ward or receiving-room manual.

The Growth of Scientific Physiology

Physiological Method and the Mechanist-Vitalist Controversy, Illustrated by the Problems of Respiration and Animal Heat. G. J. GOODFIELD. London: Hutchinson. 1960. Pp. 162. 18*s*.

THE story of how the problems of respiration and animal heat were unravelled is an interesting one and demonstrates clearly how much an advance in one aspect of science depends on progress in others. It also shows how easily a correct observation can, in the absence of sufficient information, lead to incorrect deduction. The moral of this is that correct observation is extremely important and that no-one need be ashamed of altering a hypothesis when data change. From the earliest times it was obvious that respiration and life and thus, for warm-blooded animals, heat were inextricably linked. The discovery of the atmospheric gases and the finding that oxygen was taken into the body and carbon dioxide lost from it forwarded knowledge to some extent, but even as late as 1856 some scientists were still asking whether it was not in the lungs themselves that combustion took place. Further advance depended on the development of organic chemistry and the realisation that the composition of organic substances and those found in living creatures was similar. Nevertheless, this finding still left the vitalists in a strong position. The author points out that Liebig himself was a vitalist, a fact not commonly appreciated since this view is best shown in his book *Animal Chemistry*, which is read less often than his other works.

One of the most important facets of the work of Claude Bernard was his understanding that chemical processes in living organisms were similar to those in non-living systems, but appeared different because of the infinitely complex compensatory mechanisms whereby the internal environment was maintained within relatively small limits. This point of view combined and largely explained away the differences between the mechanists and vitalists. This small book clearly and interestingly describes and discusses the many opposing theories, each of which was to some extent founded on observation. The bibliography includes useful short biographical notes about the lesser-known worthies whose work is mentioned.

Search for Security

An Ethno-psychiatric Study of Rural Ghana. M. J. FIELD, M.B., PH.D. London: Faber & Faber. 1960. Pp. 478. 42*s*.

STUDIES of alien cultures are common enough but too often they are disappointingly superficial. Realising that a grasp of psychology and psychiatry, as well as anthropology, was essential to any adequate understanding of customs in rural Ghana, Dr. Field undertook the appropriate training and is therefore able to offer a particularly valuable and authoritative (and fascinating) study derived from years of experience in the country during the 1930s and again in the 1950s.

Her short account of family structure and economic background is interesting enough, and the 146 case-descriptions that form the greater part of the book are unique and important illustrations of the way cultural factors mould the clinical features of some familiar conditions. Diagnostic grouping, however, especially the "schizo-affective", is open to argument. But Dr. Field is at her most stimulating in describing the phenomena of spirit possession and in linking, via a common origin, these trance-like states (a little too convincingly perhaps?) to the similar conduct of Biblical prophets.

The new wave of shrines was Dr. Field's primary interest—shrines usually where priests, in states of "dissociation", gave prophecies, settled quarrels, promoted social conscience, treated mental illness, and dispensed protective or other magic. The careful search by the priest for facts, especially sinful conduct, was followed by fearsome injunctions to behave well, reinforced by occult and dramatic ritual: the process is not dissimilar to a very directive type of psychotherapy, and the results are evidently quite good. The multiplication of these shrines (tenfold in Dr. Field's area since 1914) she relates to a growing sense of insecurity related to the expansion of the cocoa industry and an intensely paranoid culture. Christian missionaries will be saddened by the short account of why Ghanaians join the Church, but they may rejoice at the lively indigenous heterodox developments which Dr. Field believes have caught something of the enthusiasm of early Christianity.

Fleming: the Man who Cured Millions

ANDRÉ MAUROIS. Editor: L. E. W. SMITH. London: Methuen. 1961. Pp. 203. 12*s*. 6*d*.

A PHYSICIST left a photographic plate near a tube in which an electric discharge was taking place; a surgeon picked up an article dealing with sewage disposal; a physician encountered some children at play on a hollow log: medical progress has often been advanced by what may seem wholly fortuitous circumstances. And now that the mould spore which fell on an agar plate in a Praed Street laboratory has become as famous as the apple that fell on Newton's head, the rising generation may envisage all such progress as an outcome only of a succession of strokes of good luck—overlooking Pasteur's dictum that "Fortune favours only the mind that is prepared".

Leonard Smith, in adapting André Maurois' full-length study of Sir Alexander Fleming for young readers, is at pains to emphasise how the whole of his subject's previous life played its part in the discovery of 1928. He comments, too, on his debt to Sir Almroth Wright which Fleming always acknowledged. According to Maurois, Fleming was about to leave St. Mary's for a surgical career when Wright, to prevent a good marksman being lost to the hospital rifle team, agreed to find him work in the inoculation department. It was to Wright that Fleming owed his training in bacteriology, and it was Wright's letter, in the *Times* of Aug. 31, 1942, which first publicly proclaimed the name of the man who discovered penicillin.

Considering the youth of his readers Mr. Smith might have been less restrained about the dramatic events of the war years; about the Oxford policeman who survived only long enough to demonstrate the potentiality of the new drug and to exhaust the whole of the available supply; about the discoverer's first bold use of intrathecal penicillin for a friend who was desperately ill. But thereafter the stories of Fleming and of penicillin became the same, and are treated as vividly as one would have expected. Those to whom the book is addressed

will be delighted by it. Any of their elders who may be unacquainted with its original version will find this one such an engaging preface that they will want to have the larger work.

Clinical Anatomy

A Revision and Applied Anatomy for Clinical Students. HAROLD ELLIS, M.CH., F.R.C.S., surgical tutor, Radcliffe Infirmary, Oxford. Oxford: Blackwell Scientific Publications. 1960. Pp. 369. 37*s*. 6*d*.

THE author sets out to bridge the supposed gap between anatomy as taught in preclinical departments and what students encounter in the wards and operating-theatres, and he has tried to do this by highlighting those features which are of clinical importance, in medicine and midwifery as well as in surgery. Though Mr. Ellis seems to underestimate the approach to the subject prevalent in many anatomy departments, he can be congratulated on achieving an integration of anatomy and clinical science in a rather restricted surgical context. Much of the material is presented in what may be described as the traditional approach to surgical anatomy, and so lacks some of the vitality that might have been achieved by a greater emphasis on the relation of structure to function.

A number of the illustrations are unsatisfactory (e.g., fig. 6 in which the relations of the cervical nerves to the vertebræ are incorrect). In the surgical anatomy there are some unexpected omissions, such as the absence of any mention of the anatomical basis of abdominal pain, and of the functions of the abdominal musculature. Mr. Ellis's account of the palmar spaces is not the one generally accepted. Obstetricians will not be satisfied with the dismissal of the transverse perineal muscles without any function being ascribed to them. The pituitary is absent from the index and the text, and there is no reference to the structural features concerned with the filling of coronary arteries and to the structures involved in bronchial spasm and the overcoming of it.

Quellen medizinischer Literaturangaben und Methodik ihrer Bearbeitung

GÁBOR INKE, M.D., chief, Anatomical Institute, University of Halle. Jena: Gustav Fischer. 1960. Pp. 165. DM 11.10.

This little book can be recommended not only to medical librarians and research-workers but also to anyone who wants a guide to the intricacies of medical bibliography and cataloguing. It should help to develop the detective instinct often needed to track down obscure or incomplete references.

The first part of the book deals with medical bibliographies and source-books. The lists of them are comprehensive and international and include the periodical indexes that have ceased publication. In addition, there are lists of periodical and occasional bibliographies of specific branches of medicine and the allied sciences. The methods of abbreviating titles used in the *World List of Scientific Periodicals* and *World Medical Periodicals* are explained and listed alphabetically. The indexing of authors' names is described briefly. The sources from which microfilms and microcards may be obtained are given. The suggested wording for reprint-request cards in eight languages, including Latin, may not appeal to some of the correspondents who have been discussing this subject in our columns lately.

The second part sets out methods of classifying and cataloguing articles and reprints. These methods range from simple record cards and notched cards to punched and slotted cards suitable for machine sorting and classifying. The types and sizes of cards illustrated conform to the Deutsche Industrie Normen, but the methods are equally applicable to the cards of sizes and shapes more familiar in this country.

There are two sets of references to books and journals—one on bibliographic methods and the other on classifying and indexing. The references are to work published in all parts of the world.

Though the text is in German, only a slight knowledge of the language is needed to obtain a great deal of useful information from this book.

Memories of a Doctor in War and Peace

ISABEL HUTTON, C.B.E., M.D. London: William Heinemann. 1960. Pp. 348. 25*s*.

Lady Hutton, who died last year, was well known as a writer, and her book, *The Hygiene of Marriage*, is still widely read. It was first published in 1923, courageously, by Heinemann. At that time its subject, the technique of marriage, was taboo and there was a real risk of its being suppressed with ignominy. In these memoirs, Lady Hutton has described the tremendous changes that took place in her lifetime, not only in medical practice and medical outlook but in other ways. This book will be of special interest to women doctors, since it gives a clear account of the author's early career and of the part which she and other women doctors have played in the events of this century.

Injuries of Brain and Spinal Cord and their Coverings (4th ed. London: Cassell. 1960. Pp. 739. 140*s*.).—A fourth edition in 20 years of this well-known book by Prof. Samuel Brock, of New York, speaks well for its popularity. There are two new chapters on meningitis and on the bladder in paraplegia. Some chapters have been rewritten, and others have an addendum on recent advances. There is no doubt that rewriting is worth while: of mere added notes, " c'est magnifique mais ce n'est pas la guérison ". Several sections must be considered together—for example, the chapters on psychoneurosis and malingering with the organic neurological sequelæ. None should be read without reference to the introduction by the editor. Some fundamental points are still controversial, such as the cause of loss of consciousness in concussion. The chapter on this subject expresses favour for a holistic paralysis, whereas other authors, including Professor Brock himself, lean towards focal dysfunction in the brain-stem. In other respects this chapter, though a classic of clinical description, has a dated air. " Centres ", highest or otherwise, have been out of favour in physiological circles this many a year. For the rest of the book there are good solid pieces of writing on complications, traumatic sequelæ, cerebral birth injuries, and prolapsed disc. There are gems of description, as on how to outwit a malingerer, or the psychodynamics of traumatic neurosis. One notable omission is an adequate account of the clinical features and treatment of psychomotor epilepsy. It may be noted, too, that operative treatment of discs is still through a " keyhole " and that the number of patients requiring spinal fusion is consequently high. Already this book is reorienting itself in response to the reticular formation. In the future we hope to see it incorporate—not merely interpolate—the limbic cortex, its connections and its epilepsies, and discuss the place of hypothermia. The book is so good that it should be in the possession of everyone concerned with the management and assessment of injured people; it should be read as an education by all postgraduate clinical students; and it should be available for reference to surgical students at all levels.

Health in Childhood (Harmondsworth, Middlesex: Penguin Books. 1960. Pp. 237. 5*s*.).—According to the foreword, Prof. R. W. B. Ellis's book is " written essentially for ' the man in the street ' ", but it should not be confused with the majority of popular books on medical subjects. It is a straightforward undramatic account of childhood as related to health and disease. The known facts and important concepts are set out without overmuch technicality, although even the " intelligent " layman unversed in medical terminology may not be entirely happy. While the book necessarily involves much simplification and generalisation, it is not anæmic and there are many thoughtful and thought-promoting conclusions. Occasionally there is a tendency to describe details which would be more suitable for a textbook. It can be recommended unreservedly to doctors, medical students, and all those professionally concerned with the welfare of children. Furthermore it has the great merit that it will do no harm if put into the hands of even the most anxious parents. The production is excellent and errors scanty, and at 5*s*. it represents a colossal bargain.

THE LANCET

LONDON 18 MARCH 1961

Commemoration and Action

IT is over thirty years since Fleming reported his discovery of penicillin, and about twenty since Florey and Chain and their colleagues at Oxford translated that discovery into practice. Though their work has spoken for itself, and to all nations, it should have formal commemoration too. The Fleming Memorial now announced will be a magnificent national and international tribute to the people who achieved a medical revolution: and it will also be a practical means of promoting the kind of research most likely to bring further progress.

The conditions of such progress are changing. The medical scientist still forms his hypotheses and tries to test them by experiment; but few outsiders perhaps recognise how seriously he may be limited in his effort. Nowadays advanced scientific work can seldom be done except by those who have an appropriate organisation. As knowledge increases, the investigator needs longer and longer training, yet his range of competence grows narrower; and there is very real danger that, at some interesting point in his researches, he may find himself unqualified to pursue them further. Here the answer is obviously the creation of interdisciplinary teams, whose members have between them skill and equipment for following a valuable seam even when it diverges unexpectedly. Though sometimes such a team can be improvised for its task, this cannot be done unless the necessary people are trained and available: in other words it cannot be done unless someone has shown foresight. One may fairly say that if we want brilliant minds to use their opportunities, the chief necessity is to make research a reasonably secure career: those engaged in it must not feel that, for the sake of their families, they ought to be doing something else. But there must also be enough money, in the right place at the right time, to pay for investigations.

In this country support for research has come mainly from the Government, from industry, and from private gifts to individual institutions or projects; but latterly the role of the Foundations has become more important. More flexible than their Governmental counterparts, they are more interested than industry in basic research; and they can also support research in universities, whose own resources tend to be swallowed up by education. At present there are not enough independent Foundations; and nothing could in fact be more useful than the new one formed by the Fleming Fund with its two main objects —first, to provide necessary support for work by any " basic medical research institution or individual medical scientist ", and secondly to support men of outstanding ability by the creation of national and international fellowships. Naturally and rightly, two institutions whose needs the Fund will have particularly in mind are the Wright-Fleming Institute of Microbiology at St. Mary's, where Fleming worked, and the Sir William Dunn School of Pathology at Oxford, where penicillin was purified and made clinically usable.

The success of such a project depends both on the amount of money raised and on the wisdom with which that money is distributed. Though the initial appeal in this country is for only £1 million—the income on which would do no more than finance the work of 20–25 senior scientists—we must hope that the request (which is " once and for all ") will in fact bring a far more generous and useful response. This appeal provides an opportunity for us all, in large ways or small, to express our pride in one of the great achievements of our generation. The names of the sponsors—headed by Queen Elizabeth the Queen Mother as patron, the chancellors of Oxford and Cambridge as vice-patrons, and Lord Birkett as president—must convince the public that this is a deeply serious undertaking; and the professions can have equal confidence in the board of seven trustees who will allot the money: with Lord Heyworth as chairman, they include Sir Lindor Brown, Sir Hans Krebs, and Prof. P. B. Medawar. For a fund which is to aid research, particularly in biochemistry, microbiology, and pathology, the members of the scientific advisory committee are equally appropriate—namely, Sir Charles Dodds (chairman), Prof. A. Neuberger, Prof. G. Payling Wright, Prof. L. S. Penrose, and Sir George Pickering.

This week has seen the launching of the British appeal. The sponsors have good reason to hope that " men and women everywhere will wish to commemorate the discovery of penicillin by giving support to the kind of research from which penicillin came ", but meanwhile Britain has the right and duty to give a lead. In England donations may be sent to 26, Upper Brook Street, London, W.1, and in Scotland to 25, Charlotte Square, Edinburgh, 2.

" Polymyalgia Rheumatica "

A MIDDLE-AGED or elderly woman is suddenly afflicted by stiffness and pain in the neck or shoulder-girdle. Soon afterwards similar symptoms affect the muscles of the buttocks and thighs, movement at the shoulders is impaired, weight and appetite decline, mild fever develops, and the patient becomes depressed and miserable. Muscular stiffness, most pronounced on waking, may be severe enough to prevent her from sitting up in bed or from dressing without help. Her erythrocyte-sedimentation rate rises to very high levels, and her hæmoglobin falls to the region of 60–70%. Without treatment the distressing symptoms persist for many months but eventually dwindle until no more than occasional aches remain. Two or three years may pass before the patient is once more in good health. This story is familiar to many, but the disorder is not yet recognised as an entity in any formal classification of

rheumatic disorders. GORDON [1] has described a series of cases of this symptom-complex under the title " polymyalgia rheumatica "—a term tentatively suggested by the late Dr. STUART BARBER.[2] Descriptions of what appear to be the same clinical picture have also been published under such names as " myalgic syndrome of the aged with systemic reaction ",[3] " *pseudo-polyarthrite rhizomélique* " [4] " anarthritic rheumatoid disease ",[5 6] and others.[7–11] GORDON found the first reference to the condition in a report by BRUCE [12] from Strathpeffer Spa in 1888.

Most of the published reports differ little in their description of the main clinical features. In GORDON's series men and women were equally represented, but the consensus of opinion is that women are affected three to four times as commonly as men. The onset, usually but not invariably acute, is commonly in the 7th or 8th decade of life, and the youngest patients have been in the 5th decade. The muscles or muscle-groups affected include those of the neck, shoulders, upper arms, lumbar region, buttocks, and thighs. Symptoms start as often in the pelvic girdle as in the shoulder region, but the latter is always affected at some stage. Restriction of movement is less often apparent in the hips than in the shoulders or neck. GORDON found tenderness in the affected muscles and in the periarticular tissues of large joints; but clinical evidence of true myositis is lacking, and disability is due to stiffness rather than to muscular weakness. In contrast to the commonly acute onset, the stage of improvement is characteristically lengthy and may be interrupted by exacerbations. Besides the accelerated erythrocyte-sedimentation rate (figures in excess of 100 mm. by the Westergren method are characteristic) and the moderate anæmia, laboratory tests reveal few abnormalities and none which is any way specific. The serum-albumin and α_1, α_2, and sometimes γ globulin tend to be increased; and, according to BAGRATUNI,[5 6] the fibrinogen level, always raised, may exceed 900 mg. per 100 ml. The leucocyte-count is usually normal.

Divergences in descriptions of the syndrome concern mainly the presence or absence of arthritis. BAGRATUNI, in support of his view that the syndrome is a variant of rheumatoid disease, records among his 17 cases 4 instances of transient joint swelling as well as 3 of skin nodules and a few of rashes; furthermore the Rose-Waaler test was positive in 7. GORDON found swollen joints in 6 of his 21 cases: the knees were most commonly involved, but occasionally some of the small joints of the hands were affected. Among 13 cases KERSLEY [3] found slight swelling of the hands or knees as a late development in 3. BARBER, on the other hand, did not encounter any evidence of arthritis in his cases. The experience of other observers has been that brief episodes of joint swelling—sometimes including effusions in the knees—are not uncommonly found if patients are kept under close observation. It is difficult to judge the significance of BAGRATUNI's nodules since he gives no details of their site or clinical characteristics: demonstration that these lesions had the histological characteristics of rheumatoid nodules would have greatly strengthened the case for identifying polymyalgia as a form of rheumatoid disease. The serological case for identity is conflicting: BARBER and GORDON reported negative Rose-Waaler tests: BAGRATUNI's threshold for a " strongly positive " result is low by the standards of most laboratories. There is, too, evidence that a *transient* positive test may be found in some non-rheumatoid conditions, such as erythema nodosum.

Discussion of the possible rheumatoid character of polymyalgia raises questions of semantics. BAGRATUNI described " rheumatoid " as a non-committal adjective —a view justified more by etymology than by current usage. He held that the crippling muscular pains and good prognosis set the syndrome as he described it apart from the group comprising systemic lupus erythematosus, polyarteritis nodosa, dermatomyositis, and scleroderma; and that the same features, together with the age of onset, placed it in the rheumatoid group. The first part of this proposition is more easily accepted than the second; for a uniformly good prognosis is not a hallmark of rheumatoid disease as most people understand it, and the peak incidence of polymyalgia falls at a rather later age than that of rheumatoid arthritis. KERSLEY (though with much greater reserve) agreed that the syndrome might be related to rheumatoid disease. Certainly at some point in the illness, particularly if symmetrically located joints become swollen, it will often be difficult to deny that this may be the correct diagnosis. The strongest evidence for the contrary view is the concurrence of a very characteristic mode of onset with a good prognosis, the brief duration of true arthritis, and the invariable absence of late deformities or erosive lesions in the joints.

In its early stages polymyalgia rheumatica has to be distinguished from many other disorders—including myelomatosis, carcinomatosis, " frozen shoulder ", cervical and lumbar disc degeneration, brucellosis, senile osteoporosis, and generalised osteoarthrosis. One or both of these last two commonly accompany polymyalgia rheumatica, though it has not been suggested that they are pathogenetically related. Perhaps the outstanding threat to the patient's welfare is that the doctor, contemplating a dejected and miserable being with pains " all over ", neglects to have the erythrocyte-sedimentation rate measured and attaches the tenacious label " psychoneurosis ".

In treatment BARBER and GORDON found analgesics only moderately helpful, but anti-inflammatory steroids very effective. According to GORDON short courses may suffice, and though they may have to be repeated full relapse on withdrawal is not as invariable as it is in rheumatoid arthritis. KERSLEY reached a similar conclusion.

1. Gordon, I. *Quart. J. Med.* 1960, **29**, 473.
2. Barber, H. S. *Ann. rheum. Dis.* 1957, **16**, 230.
3. Kersley, G. D. *Congr. Europ. Rhum.* 1951; p. 388.
4. Forestier, J., Certonciny, A. *Rev. Rhum.* 1953, **20**, 854.
5. Bagratuni, L. *Ann. rheum. Dis.* 1953, **12**, 98.
6. Bagratuni, L. *Lancet*, 1956, ii, 694.
7. Meulengracht, E. *Nord. Med.* 1945, **27**, 1569.
8. Meulengracht, E., Schwartz, M. *Acta med. scand.* 1952, **143**, 350.
9. Holst, J. E., Johansen, E. *ibid.* 1945, **122**, 258.
10. Porsman, V. A. *Congr. Europ. Rhum.* 1951; p. 479.
11. Bevan, F. A. College of General Practitioners, Research News Letter, 1955, no. 9, p. 157.
12. Bruce, W. *Brit. med. J.* 1888, ii, 811.

Despite several careful studies polymyalgia, if it ranks as a distinct entity, does so only as a clinical symptom-complex recognisable by no pathological lesion or specific laboratory test. GORDON examined biopsy specimens from the deltoid muscle in 6 cases: muscle-fibres were normal in all; but, of 2 specimens in which muscular septa were included, these showed in 1 instance collections of chronic inflammatory cells related mainly to dilated vessels, and in the other small collections of lymphocytes distributed around vessels in both fibroconnective tissue and fat. BAGRATUNI described slight lymphocytic infiltration of the dermis in 1 case. Neither worker attached much significance to these abnormalities. KERSLEY examined specimens of muscle from 4 of his cases, with negative results. As yet unproved histologically, but attractive enough to warrant further study, is the hypothesis of PAULLEY and HUGHES [13] that polymyalgia rheumatica is one manifestation of giant-cell arteritis. Certainly the rheumatic symptoms of giant-cell arteritis presenting as classical temporal arteritis can closely resemble those of polymyalgia rheumatica and may antedate recognisable clinical changes in the cranial vessels. Moreover there is now ample evidence for the concept of giant-cell arteritis as a generalised systemic disease which may spare the cranial vessels and which cannot be confirmed by random muscle biopsy. Pathological changes may be confined to the aorta, and coronary, carotid, intracerebral, and meningeal vessels. That blindness does not supervene in polymyalgia rheumatica may denote only that this diagnosis is made in cases of giant-cell arteritis when sparing of the temporal and ophthalmic arteries obscures the true nature of the condition. This hypothesis provides one avenue for the experimental approach to a relatively common illness which is likely to be diagnosed increasingly as its features become more widely recognised.

Prevention of Hospital Infection

HOSPITAL pathologists and bacteriologists have never failed to emphasise that hospital infection can be most effectively prevented and controlled by an aseptic discipline based on a realistic understanding of how to apply bacteriology to clinical practice. From about 1918, when the hæmolytic streptococcus was the organism that caused most concern, new insight into hospital epidemiology has come from studies made by so many bacteriologists and clinicians that it might almost seem wrong to name any one in particular. The editorial board of the *Journal of Clinical Pathology* will nevertheless command approval for having devoted an issue [14] wholly to hospital infection and for having dedicated it to Dr. LEONARD COLEBROOK for his pioneer work on hospital cross-infection. Quite certainly, COLEBROOK and his immediate collaborators would wish to name many contemporaries of the early and middle '20s who independently made notable contributions to the early efforts to increase understanding of how the hæmolytic streptococcus could be controlled. We remember such names as those of the DICKS, DOCHEZ, AVERY, LANCEFIELD, EAGLES, BLISS, GORDON, JOHN SMITH, and FRANK GRIFFITH, all of whom did work which has proved fundamentally important. But COLEBROOK deserves honour not only as one of the pioneers, but as the greatest persister. Throughout some thirty-five years of exacting work on the streptococcus, puerperal sepsis, the sulphonamides, war wounds, burns, industrial injuries, antibiotics, and the current hospital plague of antibiotic-resistant organisms, COLEBROOK has steadily remained a reliable source of wise advice, new thoughts, and persuasive exhortation.

In the special issue MARY BARBER argues convincingly that hospital infection can be prevented if enough people take it seriously. KNOX makes it clear that failure to sterilise is widespread, and that the consequences can be serious. He emphasises that hospital infection spreads by many channels and that effective sterilisation is only one of the ways by which its incidence may be reduced. BLOWERS, reviewing ward management, suggests methods which set minimum standards for dealing with isolation, infection from the staff, environmental contamination, wound dressing, and so forth. GILLESPIE shows that chemical disinfectants, properly selected and sensibly used, still have a place in interrupting some of the routes by which infection spreads. BATE finds that floor-cleaning methods merit bacteriological scrutiny and that the choice of vacuum cleaners should not be conditioned solely by their outward appearance. DARMADY, HUGHES, JONES, PRINCE, and TUKE show that dry-heat sterilisation has more applications than have been generally recognised. They describe a new method of using dry heat in a nearly perfect vacuum as a means of sterilising operating-theatre instruments; this may be particularly useful where a steam supply is not readily available. SHOOTER and WILLIAMS lay down intelligent and readily intelligible views on operating-theatre design and practice in so far as they affect the prevention of infection. Their article might raise only one critical question: are there indeed any reasons so "absolutely compelling" that a surgeon with sepsis might operate? In the light of reported disasters from such a source we are inclined to doubt the wisdom of any relaxation.

HOWIE reviews recent work which shows that surgeons' autoclaves have been too readily accepted as reliable and efficient. His article describes the principles that underlie successful autoclaving and suggests that education and supervision may be an important duty of the hospital bacteriologist. Sterilisation by radiation can be highly efficacious, and the practical issues are set out very clearly by DARMADY, HUGHES, BURT, FREEMAN, and POWELL. KELSEY hopes that ethylene-oxide sterilisers will be situated only where they can be operated both economically and safely; they are not suitable for widespread use in small hospitals or isolated units. PATRICK, WHARTON, PRENTIS, and SIGNY are impressed by the efficacy of a forced-convection gas-fired oven, which will sterilise a very heavy load of syringes and instruments and containers. DARMADY, HUGHES, JONES, PRINCE, and VERDON have used a standard dish-washing machine fitted with an automatic cycle to clean and disinfect bedpans. WELCH examines different possible forms of organising central sterile supply departments and supplies answers—not all of them necessarily final—to a great many of the questions

13. Paulley. J. W., Hughes, J. P. *ibid.* 1960, ii. 1562.
14. *Journal of Clinical Pathology*, 1961, **14**, no. 1 (January). Single copies (17*s.* 6*d.*) are obtainable from the publishers, the British Medical Association, Tavistock Square, London, W.C.1.

which urgently need answers. ALDER and ALDER have examined bacteriologically the protection afforded against recontamination of surgical packs by different wrapping materials. A thick crepe paper proved better than calico and balloon-cloth fabrics. Paper packs in paper-lined cartons had many advantages in regard both to the protection they afford and to convenience in transport and storage. LARKIN, BRIDSON, GRIEVE, and GIBSON have found that simply immersing blankets in 0·5% solution of 'Hycolin' (a mixture of halogenated alkyl/aryl phenols) at 45°C for 10 minutes disinfects hospital blankets without harming their fabric. LOWBURY has managed to assess methods of skin disinfection by validly objective criteria. He found that 0·5% chlorhexidine in 70% ethyl alcohol, which is entirely acceptable even to delicate skins, was not only highly effective but as good as 1% iodine in alcohol, which harms many skins. Under ward conditions VERDON made efficiency tests on eleven common skin antiseptics, including 1% iodine in 90% spirit but not chlorhexidine in alcohol. From these tests 'Laurolinium' (1% or 5%) emerged as the most effective. BRADLEY and MEYNELL supply some interesting information, along familiar lines, about the identity and antibiotic resistance of staphylococci isolated in hospital practice in Birmingham. Phage-type 80 accounted for 10% of 500 inpatient strains and 4·5% of strains in 492 casualties; of these 492 strains 61% were penicillin-sensitive, compared with only 23% of the 500 inpatient strains. WESLEY-JAMES and ALDER, comparing 123 cultures of *Staphylococcus aureus* isolated from septic fingers with 124 strains from the noses of healthy volunteers, found that certain strains, notably those with phage patterns 80 and 52A/79 together with some group-II strains, were comparatively numerous in septic fingers and were undoubtedly associated with unusually severe lesions.

An editorial reasonably describes the volume as a reminder and an encouragement to those who should be responsible for the bacteriological safety of patients in hospitals. Indeed, this is perhaps too modest; for the editorial board of the *Journal of Clinical Pathology*, in justly honouring LEONARD COLEBROOK, has made a significant contribution of its own towards the prevention of hospital infection.

Annotations

HOSPITAL AND RESEARCH CENTRE

NEW hospitals in the London area are not so common that news of them is dulled by familiarity. The choice of Northwick Park for the new Harrow District Hospital is more than satisfactory; for the site is a fine one yet easily accessible. This is the more important because, as the Minister of Health announced on Monday, the hospital is to be associated with the Clinical Research Centre which the Medical Research Council is to establish.[1] This is to be provided out of a special allocation by the Treasury, and the new plans for Northwick Park clearly fall into line with the Council's idea that the " research centre should form an integral part of a hospital dealing with current medical problems and thus keep in touch with trends and changing disease patterns in day-to-day medical practice".

The patients in the Clinical Research Centre will naturally be fewer than those in the district hospital, but eventually it may have as many as 200 beds, which would permit a very wide range of studies. Probably a smaller number—perhaps half—will be equipped in the first place; but one can imagine even within this smaller figure some 8–10 " units ", each paying particular attention to a special problem. Clearly it is too early to be defining these problems exactly; no doubt the choice will be made partly upon current social needs and partly upon the likelihood of gaining new and useful knowledge and hence better means of treatment. Already, under the National Health Service, we in this country have exceptional opportunities for observing those patients whose illnesses make them ill for long periods. Another factor which will no doubt influence the choice of a research topic will be the availability of physicians, surgeons, pathologists, and others who are going to undertake this kind of work. Again, many good judges believe that we have in the United Kingdom today some remarkably able men and women with the training and aspirations necessary to make a success of clinical research. It will be surprising if, in years to come, the new Harrow hospital, and those who use it, do not regard their association with the Medical Research Council as a piece of medical good fortune, ensuring the highest standards in every way.

In recognising the need for the Clinical Research Centre and wishing it success, we should like to see it starting work tomorrow. Evidently, however, the choice of the Northwick Park site implies the creation of special facilities in the way of new wards, laboratories, residential accommodation for nurses and medical assistants, and much else, entirely from scratch. Those who have already been concerned with planning new hospitals will know that this is a considerable undertaking, and those who have not can read about it in the Oxford Regional Hospital Board's *Commissioning a New Hospital*, on the Princess Margaret Hospital at Swindon.[2] But every effort will be made to avoid unnecessary delay, and those planning the new district hospital and the Clinical Research Centre will be able to draw on much expert advice. As was announced at the end of last year, the director of the centre will be Prof. John Squire.

PSYCHIATRIC EPIDEMIOLOGY

THE success of epidemiological methods in helping to understand and control infectious disease has rightly led to their application in other disorders. In psychiatry, vital statistics are much harder to disentangle and validate, though people have been trying to do so since the late nineteenth century; and recent progress with population surveys in such conditions as lung cancer and coronary thrombosis has added vigour to an expanding effort.

A signpost to this little-charted segment of psychiatric research has lately been erected by Prof. D. D. Reid, whose terse and admirable monograph [3] deserves careful study. Not only does he describe the methods and the practical problems in their use, but also, in showing how the discipline has evolved, he contrives to give a bird's-eye view of most of the more fruitful publications. The fullest application of these techniques must wait upon advances in clinical psychiatry, especially upon an agreed

1. Annual report of Medical Research Council for 1958-59, p.7. See *Lancet*, 1960, ii, 193.

2. See *Lancet*, March 4, 1961, p. 517.

3. Epidemiological Methods in the Study of Mental Disorders. By D. D. REID, M.D., D.SC., M.R.C.P., professor of epidemiology, London School of Hygiene and Tropical Medicine. World Health Organisation. Public Health Paper no. 2. Geneva. 1960. Pp. 79. 5s. Obtainable from H.M. Stationery Office, P.O. Box no. 569, London, S.E.1.

and valid scheme of diagnostic classification. Another problem has been the distressing way in which the results of years of work melt away before the two crucial words "so what?". But where clear criteria, such as suicide, fertility, hospital admission, or breakdown under operational stress in war, can be applied, the background knowledge so far gained is greater than most people realise, and Professor Reid's paper is far from discouraging. Useful correlations emerge from this approach, albeit as pointers, more often than not, to areas of further study: the new report by Wilkins,[4] who used the "crime wave" to show that the origins of delinquency may lie between the ages of 4 and 6, is a good example. Other recent clues can be found in the General Register Office's morbidity statistics [5]—for example, that farmers are the least neurotic members of the community while professional and administrative workers seem much afflicted. Then there were the interesting observations of differences in mental-hospital admission by area,[6] which could reflect all sorts of things.

Population studies carry a high priority, but those related to mental-hospital admission (as so many have been) are clearly fraught with imponderables: basic knowledge requires a basic approach—at the community level. Studies in general practice offer such an approach, though a treacherous one, since events in an individual practice must be determined in large part by the personality of the practitioner. His sympathy and tolerance, for example, must influence the numbers of neurotics on his list and the demands they make upon him. Again, most studies relate to consultations only (i.e., to manifest prevalence) and take no account of patients who put up with their disorder alone, or seek help elsewhere. These factors, added to difficulties in classification, have led to astonishingly divergent estimates of incidence; Paulett,[7] for example, diagnosed neurotic symptoms without organic disorder in 70% of his patients over a 5-year period, and he believed that a long-term study would probably show that everyone suffered thus at one time or another during their life. Other estimates, however, have judged neurosis to be as low as 2%.[8] Ryle [9] has lately reviewed the subject and found a 9·4% annual prevalence in his practice of anxiety states, hypochondriasis, and endogenous depression. Hopkins [10] believed that psychiatric illness had an incidence of 11% per year, and the other eight general-practitioner surveys he mentions ranged between about 7% and 17%. All the more surprising was it, therefore, that the Registrar-General's survey,[5] embracing 106 practices, gave a figure of over 18%.

Approaching the matter in rather more detail, Kessel [11] has studied cases in a large London group practice which Stein [12] had shown to be stable and representative. He classified all on a defined scale of morbidity, and the one-year prevalence-rate for mental, psychoneurotic, and personality disorders (International Classification of Disease category V) came out at only 5% (3·3% for men and 6·8% for women). Some 9% of the practice, however, had attended for illnesses which revealed "conspicuous psychiatric traits"—the difference between 5% and 9% being accounted for by those presenting with physical symptoms (with or without established disease) which would therefore be classified differently on the I.C.D. An extra 5% had personality defects not associated with the presenting illness. The 9% with "conspicuous psychiatric morbidity" accounted for 23% of all consultations (only half of which related to their psychological illness), but only 1 in 10 was referred to a psychiatrist.

Taking in those conditions (such as insomnia or dyspepsia) where physical cause had been excluded, the numbers jumped to 38%, and adding "psychosomatic disorders" gave a grand total of 52%. "This", as Kessel points out, "is clearly a ridiculous state of affairs", and one which indicates very forcibly the need for agreed operational definitions in any work of this sort.

4. Wilkins, L. T. Delinquent Generations. H.M. Stationery Office, 1961. See *Lancet*, Feb. 4, 1961, p. 267.
5. General Register Office: Studies on Medical and Population Subjects, no. 14: Morbidity Statistics from General Practice, vol. II (Occupation). H.M. Stationery Office, 1960. See *Lancet*, 1960, ii, 377.
6. General Register Office: Studies on Medical and Population Subjects, no. 16. Areas of Residence of Mental Hospital Patients. H.M. Stationery Office, 1960. See *Lancet*, 1960, ii, 1396.
7. Paulett, J. D. *Lancet*, 1956, ii, 37.
8. Taylor, S. *Med. Wld, Lond.* 1954, **81**, 137.
9. Ryle, A. *J. Coll. gen. Pract.* 1960, **3**, 313.
10. Hopkins, P. *Postgrad. med. J.* 1960, **36**, 323.
11. Kessel, W. I. N. *Brit. J. prev. soc. Med.* 1960, **14**, 16.
12. Stein, L. *ibid.* 1960, **14**, 9.

DIAGNOSIS OF BONE TUMOURS

MALIGNANT bone tumours have always had a bad reputation, and the prognosis of osteogenic sarcoma is particularly bad. Rowland et al.[1] report a five-year-survival rate of 18% in 106 proved cases treated by amputation. These workers advocate biopsy below two tourniquets, the diagnosis being made from a frozen section, and (when indicated) immediate amputation between the tourniquets.

Unfortunately, tumours do not always fall into clear-cut divisions. One part of a tumour may differ considerably from another part, and examination of a small fragment may be misleading. Furthermore it is not always easy to differentiate between malignant cells and rapidly growing new cells, as in callus. Because of these difficulties, other diagnostic methods have been devised. Among these is arteriography: the blood-supply to a malignant tumour is greatly increased, and the venous drainage is rapid.

In 1957 Rall et al.[2] noted that the fluorescence which tetracyclines impart to all tissues is greatly increased in bone, being especially pronounced in growing bone and even more distinct in malignant bone tumours. The cause of this fluorescence, which except in bone is slight and transient, is not known for certain; but unaltered tetracycline or a metabolic derivative of it is generally believed to bond to the calcium or matrix of bone; and Milch et al.[3] suggested that this feature might be used in the diagnosis of malignant bone tumours.

McLeay and Walske [4] have attempted to estimate the concentration of tetracyclines in different types of bone. For three days before operation the patient was given 15 mg. of oxytetracycline per kg. body-weight intramuscularly in 100 ml. of saline solution in divided doses; the administration was stopped twelve hours before operation to allow time for the drug to be removed from the normal tissues. When the bone was exposed it was illuminated by an ultraviolet 100-watt lamp, all other lights being turned out. The tumour could be seen sharply demarcated so that a biopsy could be taken from the most fluorescent part. Subsequently portions of tissue were removed and studied. It was found that the fluorescence persisted almost unchanged in such a specimen for six months at −10°C, and that the bacteriostatic activity

1. Rowland, S. A., Dahlin, C., Hayles, A. B., Sullivan, C. R. *J. Amer. med. Ass.* 1960, **174**, 489.
2. Rall, D. P., Loo, T. C., Montagne, L., Kelly, M. G. *J. nat. Cancer Inst.* 1957, **19**, 79.
3. Milch, A. R., Rall, P. D., Tobie, E. J. *ibid.* p. 87.
4. McLeay, J. P., Walske, B. R. *J. Bone Jt Surg.* 1960, **42A**, 940.

of the oxytetracycline was also unchanged. This activity was tested against standard concentrations of oxytetracycline using a standard organism to determine the quantity deposited in the tissue. The concentration of oxytetracycline in bone tumours was found to be ten times as great as that in normal new bone. Fractures and osteomyelitis showed no increase, but in a case of Paget's disease brilliant fluorescence was noted (no biopsy was done in this case).

This line of investigation may prove valuable not only for diagnosis but also possibly for treatment. McLeay et al. suggest that oxytetracycline might be used as a vehicle to convey radioactive isotope in high concentration to the sites of bone tumours.

TOXIC CHEMICALS ON THE FARM

SOME of the comments on the report [1] issued by the Royal Society for the Protection of Birds on deaths of birds and mammals connected with toxic chemicals have been in language so exaggerated as to be misleading. A certain number of birds have died after eating seed corn dressed with insecticides and fungicides. The corpses have been fatal to mammals which ate them. There are grounds for suspicion that certain other chemicals used by the farmer may have killed birds. That is about as much as is known at the moment, and loose talk about " massacres " will not add to our slender knowledge of the extent and ultimate effects of these disasters.

The substances under suspicion of causing the deaths are chlorinated hydrocarbons (e.g., dieldrin) and mercurial fungicides. In mammals at any rate the former can act as cumulative poisons. Besides these some farmers—especially growers of fruit and hops—use organic phosphates chemically allied to the " nerve gases " and quite exceptionally poisonous. On far less certain evidence the selective weedkillers have had their share of blame. Arsenic (used to destroy potato haulms) has killed men and farm stock, but its use is now abandoned by agreement between the makers and the Ministry of Agriculture. This catalogue should be enough to stock the Borgias' store cupboard, but it omits many chemicals used every day on the farm without apparently harming anyone. To blame " chemicals " as such is anti-science at its worst.

The extent of the damage done to bird life by toxic chemicals is quite unknown. Except for a few species (e.g., herons) most estimates of the numbers of wild birds are guesswork, but it is obvious that the numbers fluctuate considerably for " natural " causes. We are almost equally ignorant of the causes of death of birds. There seems to be general agreement that trauma is the chief cause of death, but how many of the birds killed by chemicals would have died before long from some other cause? [2] Some of the most reliable evidence comes from game birds. After these are a few months old they live as wild birds but their numbers are known fairly accurately. Every 50 pairs of partridges produces an average of 750 eggs in May. By September only 250 chicks and 80 adults are still alive. Of these 120 are shot and 100 die in the winter, leaving about 50 pairs to begin the cycle again. We would add a guess that were none of them shot (as during the war) the population would not rise very fast. And for what it is worth the game bags in the past two years in East Anglia (where seed dressings are used more extensively than elsewhere) are said to have exceeded all recollections.

There is much work to be done in the field and in the laboratory. To find a dead bird and to smell a selective weedkiller simultaneously does not establish the cause of death. The report quotes some analyses of the organs of birds found dead in suspicious circumstances, but these lose most of their point because no normal values are quoted. Perhaps they are not known. The toxicity of these substances for birds cannot be assumed from work on mammals: dicophane (D.D.T.), for example, is extraordinarily poisonous to fish. There is a need to know as accurately as may be possible the proportion of birds exposed to a defined risk which die. As Slater has pointed out,[3] of two fields receiving the same treatment and only a few hundred yards apart, one may cause casualties and one may not. The weather, the rate of germination, and the availability of other food may each have its effect. It is an inquiry to daunt the most ingenious epidemiologist, and suggestions that these chemicals have some effect on avian fertility or even on the health of man himself must wait until we know more about the primary problem.

Even before this report was published the Ministry of Agriculture called a conference of the interested parties (including the makers of agricultural chemicals). There was general agreement that seed dressings are almost essential to agriculture and that not all seed dressings are dangerous to birds. Those which contain dieldrin, aldrin, and heptachlor are, however, likely to kill birds which eat the dressed grain.[4] As a pendant to this the Ministry points out that heavy dressings of these poisons are needed only to combat bulb fly in winter wheat and suggest that for other corn lower concentrations will serve adequately. At the same time a research project is in hand which will include adequate provision for postmortem examinations and analyses. To these we would add the need for accurate quantitative observations in the field. Few amateur ornithologists will have the opportunities of the intelligent gamekeeper, but even the weekend bird-watcher will be able to help. The National Farmers' Union has promised the cooperation of its members, but we are bound to suggest that the high mortality among woodpigeons mentioned in the report puts certain temptations in their way.

VASOSEMINAL VESICULOGRAPHY

RADIOLOGICAL investigation of the genital tract has so far failed to arouse much enthusiasm in Great Britain, where it has been regarded as a method of mainly academic interest. The anatomical features, shown by vaso-seminal vesiculography, are thought to be known, while significant abnormalities caused by disease can often be detected more readily and safely by simpler means. Nevertheless our knowledge is now considerably enriched by a monograph in which Vestby [5] describes the technique of vesiculography and emphasises its value particularly in differentiating benign from malignant lesions of the prostate.

Vestby, who adopts the deferential route (descending injection of the vas exposed at the scrotal neck), insists on the importance of using a suitable non-viscous water-soluble contrast material, and of taking films during the

1. The deaths of birds and mammals connected with toxic chemicals in the first half of 1960. Royal Society for the Protection of Birds, 25, Eccleston Square, London, S.W.1.
2. Jennings, A. R. *Times*, March 3, 1961.
3. Slater, W. *New Scientist*, March 2, 1961, p. 531.
4. Ministry of Agriculture, Fisheries and Food. M.A.F.F. Dec. 21, 1960, no. 4.
5. Vestby, G. W. Vaso-seminal Vesiculography in Hypertrophy and Carcinoma of the Prostate. *Acta radiol., Stockh.* 1960, suppl. 199. Oslo: University Press. 1960. Pp. 194.

injection. The degree and order of filling of structures can thus be observed; and this information may be useful in differential diagnosis. In prostatic hypertrophy, for example, passage of the medium is often resisted at the level of the verumontanum with consequent dilatation of the proximal ejaculatory duct. In cancer, on the other hand, the ducts are usually compressed and displaced and the vesicles later become obstructed or obliterated by spread of the growth. In early cases of cancer (and it is in these that the technique is probably most valuable) the contours of the ejaculatory ducts become rigid and inelastic, and the normal circular mucosal folds are lost.

By this technique Vestby established the diagnosis in 169 of 181 cases of benign prostatic hypertrophy, and in 34 of 49 cases of prostatic cancer; there were no false positives among these 49 cases, which included some in which the diagnosis was otherwise insecure. Vestby reiterates that vasoseminal vesiculography may be of value as a test of radical operability in early cancer.

THE FERROPHAGOUS BOVINE

THE ostrich is reputed to swallow almost anything, and heraldically is often shown holding a horseshoe in its beak. Like all birds, the ostrich must have grit in its gizzard, and, together with pebbles, it will swallow any small metallic objects that are lying about. As a rule, it comes to no harm, though at least one ostrich at the London Zoo died from copper poisoning, the result of swallowing pennies fed to it by visitors. Silver—and probably cupro-nickel—coins seem innocuous.

Accounts of " human ostriches " find their way into most textbooks of gastric surgery,[1] and are usually accompanied by photographs of the astonishing collections of ironmongery recovered by gastrotomy. Some small objects undoubtedly pass completely through the intestinal tract in these people, but, possibly because of irregular outline and sheer weight, many are retained in the stomach.

Apart from veterinary surgeons and farmers, few people realise either the variety of things swallowed by cattle or the loss that results.[2] Some thirty-five years ago a famous prize bull died from peritonitis because a $21\frac{1}{2}$-in. length of wire penetrated the wall of the stomach. This was an unusually long piece of wire to be ingested, but cattle have been known to swallow carving-knives and umbrella ribs. The most dangerous foreign bodies are nails and short pieces of wire; they almost always fall into the reticulum, and, after perforating the stomach wall, give rise to peritonitis or pericarditis. Because of its apparent fondness for metallic objects, the ox in the United States has been called the " ferrophagous bovine ", and traumatic gastritis is colloquially known as " hardware disease ".

75% of cattle more than 5 years old have metallic foreign bodies in their stomachs. Some idea of the loss to the farmer can be gained from the records of the Meat Inspection Division of the United States Department of Animal Husbandry. In six months, 2199 beef carcasses were condemned because of pericarditis, 95% of the cases of which had been caused by penetrating metallic objects. No figures are available for this country, but the prevalence of traumatic gastritis is probably much the same.

Radiography of all cattle is obviously impracticable. Metal detectors, on the principle of the war-time mine detector, are widely used but have their limitations. The recently developed highly sensitive instruments that can detect tiny particles of both ferrous and non-ferrous metals would never stand the rough handling to which they would inevitably be subjected on a farm.

The disease is man-made and, because the policy of any ruminant is to eat now and chew later, the farmer must see that baling-wire is properly disposed of (or, better still, replaced by twine), and that wire fences are not allowed to disintegrate into dangerous fragments.

Various magnetic devices that can be passed down the œsophagus of cattle have proved fairly successful in extracting pieces of ferrous metal. A prophylactic method is now practised by an American veterinary surgeon. All young cattle are given orally a small cylindrical magnet which remains in the animal's stomach throughout life. There has been a spectacular drop in the number of " wire " operations—formerly about 200 a year—which he has had to carry out.

1. Crossen, H. S., Crossen, D. F. Foreign Bodies Left in the Abdomen; p. 590. St. Louis, 1940.
2. *Times*, Feb. 20, 1961.

PSYCHOGENESIS IN HISTAMINE HEADACHES

MIGRAINE presents a double problem in ætiology: why does the attack occur, and why do its vascular manifestations derive particularly from one set of vessels? In most cases of so-called histamine headache, which is generally regarded as one form of migraine, the same two problems arise. Steinhilber et al.[1] at the Mayo Clinic have investigated the personalities of patients with this type of headache.

Using the Minnesota multiphasic personality inventory they tested fifty consecutive patients with this diagnosis. They applied the same test later to fifty other patients with undifferentiated headache. In each group the proportion of abnormal personality responses was high; conversion hysteria scored high in both, and hypochondriasis especially high in the histamine cases. This contrasted with findings in general medical cases, where depressive scores were usually highest. Commenting on individual patients with histamine headache Steinhilber et al. remark on a relation between suppressed or repressed anger and headaches; and they note that the clinical impression of these patients—rigid meticulous perfectionists—was strikingly uniform. The implication of their observations is that psychological factors are important in predisposing to the headaches and in precipating attacks.

Most clinicians would agree with this. Nevertheless the findings may be biased. The groups tested were selected by attendance at hospital, which itself may have been due partly to the neurotic traits discovered in the tests, as it is unlikely that all *migraineurs* attend. Moreover in the study of the relation between emotional upsets and headache attacks mentioned in some cases, possible correlations with physical changes seem to have been ignored. If psychogenic factors are causal, as they may be, their removal should establish a cure. Investigation of this is not easy, if only owing to the difficulty of maintaining a standard emotional and physical environment. But it would be well worth undertaking at any centre where many such patients are seen. If these factors are causal they may explain the general tendency and the timing of attacks; but they still do not explain the localisation of response. Meanwhile doctors will rightly continue to apply both psychotherapy and physical remedies to patients with migraine.

1. Steinhilber, R. M., Pearson, J. S., Rushton, J. G. *Proc. Mayo Clinic*, 1960, **35**, 691.

Special Articles

GENERAL PRACTICE

Some Practical Suggestions for Reform

E. O. EVANS
M.B. Lond.

IAN MCWHINNEY
M.D. Cantab., M.R.C.P.

ALEXANDER MURRAY
M.R.C.S.

GENERAL PRACTITIONERS, STRATFORD-ON-AVON

OF all branches of medicine, general practice is the most variable. Each practice is a reflection of the character of the practitioner, the type of patient he serves, and the district in which he works. Moreover there are practically no restrictions of entry: a registrable qualification and a plate on the door and you are in. This may be good in that it promotes lusty individualism, but it is bad in that it fosters professional isolation which can cover low standards of work.

The suggestion has lately been made [1] that general practitioners in this country have failed to integrate available services for their patients' benefit, and that they cannot meet the challenge of modern medicine. We repudiate this suggestion but accept the challenge in it. Of course there is plenty of scope for improvement, and we propose a number of positive steps which we think essential if a renaissance of general practice is really to be achieved.

STATUS

General practice has become a less attractive branch of medicine, and active steps are necessary to stop this process. Isolation from hospitals, reduced opportunities for private practice or any kind of specialist work, and relatively smaller financial rewards have all added their quota. Indeed, one of the worst features of the Royal Commission's report is the very clear way in which the status of the general practitioner has been downgraded. For the first time in our history, the future consultant will be well paid throughout his apprenticeship; yet, when he has been established ten years, the full-time consultant will have a *minimum* salary of £3900 (compared with the *average* general-practitioner income at the same age of about £2700). This is a very strong financial inducement to the best brains to enter specialist medicine; but it will be a sad thing indeed if future family doctors are only those who have fallen off the specialist ladder. It is vital that a proportion of the best men should continue to be attracted to general practice as they always were in the past.

In our view, therefore, the remuneration of established and experienced doctors in domiciliary and hospital medicine should not be widely different. We agree, of course, that the larger merit awards and the higher fees for private work should mainly go to consultants, but we do not agree with the Royal Commission's apparent conclusion that the status of the general practitioner should be about two-thirds that of the specialist (para. 169 d).

Here there is little hope of any early change; but we suggest that those who are really interested in the renaissance of general practice should think and work hard and put their house in order, so that they may in future both deserve and receive greater public recognition relative to the hospital specialist.

EDUCATION

The nature and importance of general practice has long been badly taught in our medical schools: indeed it has often been misrepresented. The situation is improving, but this process would be hastened if there were more opportunities for students to learn from experienced general practitioners, and the trainee scheme might be extended to this end.

Unquestionably, the trainee scheme needs improvement. The steps needed, we believe, are (1) that it should be centrally operated; (2) that trainers should be selected by an independent committee; (3) that trainers should be adequately paid for their increased work and responsibility; and (4) that the scheme should be extended to medical students. By liaison with the university teaching centres and the College of General Practitioners, something in the nature of general-practice training centres might come about. In any event the changes should do a lot to raise the standards of general practice, for trainers also learn from their trainees and the scheme would provide another way in which a man of energy and ability could raise his income without "head-hunting". As Scott [2] has said, "if it were a privilege to be a candidate for traineeship and an honour to be a trainer, any rewards which might come to trainer or trainee would not only be deserved but would be seen to be deserved".

ENTRY TO GENERAL PRACTICE

In the past it was not uncommon for men to enter general practice immediately after qualification; but the lessons one learns as a hospital resident are invaluable and lasting and difficult to achieve in any other way.

Those who really want a renaissance of general practice will probably agree that there should be evidence of experience before a doctor is accepted as a principal in practice under the National Health Service. In view of the better pay there would be no real hardship in making three years in hospital appointments (or two years plus a year's trainee assistantship) obligatory to all new entrants. That some practical experience of midwifery should also be obtained before acceptance on the executive-council list seems equally reasonable. There may be valid arguments against such restrictions, but in the long run they would raise both the standards and status of general practice.

POSTGRADUATE EDUCATION

The most important type of postgraduate education is that which comes from constant discussion with colleagues and therefore from association with hospital doctors on the one hand and other general practitioners on the other. We shall say more of this later.

The trouble with the formal courses (which, we can testify, are excellent) is that the people who need them most are usually the most reluctant to go on them. One practical—and really quite fair—suggestion is that a locum fee should automatically be paid to doctors attending courses of over forty-eight hours. In this way there would be a subtle incentive for partners to persuade each other to go off on courses. (At present locum fees are normally

1. Forsyth, G., Logan, R. F. L. The Demand for Medical Care. Published for the Nuffield Provincial Hospitals Trust, 1960.

2. Scott, G. *Brit. med. J.* 1960, i, suppl. p. 191.

only paid to single-handed practitioners attending such courses.)

THE PRACTITIONER AND THE HOSPITAL

Closer integration of the hospital and general medical services is very necessary. One way in which this can be achieved is by giving practitioners a larger part to play in hospital life.

Diagnostic Facilities

One advantage which nationalisation could bring to all practitioners is the right of direct access to hospital diagnostic facilities. If there really are any doctors who are not competent to make responsible use of such facilities it can only be because they have been denied the right for too long.

This seems to us something which should be done *now*. If and where extra facilities are needed to make this possible, we believe they deserve the very highest priority.

Hospital Beds

Although cottage hospitals have their place in special geographic circumstances, we are inclined to agree with Fry [3] that general-practitioner beds in general hospitals are not necessarily desirable. Emotionally we all feel they would be very nice, but it is doubtful whether they are a practical possibility. In the first place, where does one draw the line? Sooner or later some practitioner with control of beds will want to start doing his own hernias, stabilising his own diabetics, and so forth. Before long general practitioners with hospital beds would be competing with consultants for the interesting cases, and the whole process would have gone full circle.

In this connection we fully support Fox's view that practitioners who have the necessary training should be allowed to do these things, but that when they do them in hospitals they should be acting as members of the consultant's team.[4]

Place of Practitioner in the Hospital

The general practitioner who wants to do hospital work should be encouraged to do so. In the first place this promotes the integration of hospital and domiciliary services. In the second place it puts back some of the specialised clinical interest which has been steadily leeched away from general practice during the past twenty years. Thirdly, with a minimum of three years' hospital experience behind him, many a practitioner will be able to perform useful functions in the hospital departments. Fourthly, attachment to and working in a hospital, and constant association and discussion of cases with specialist colleagues, is probably the finest of all forms of continuing education. In the long run we believe the hospitals will stand to gain as much as general practice will.

We recognise that such a change cannot be brought about overnight. We agree that some doctors have been isolated from hospital work for too long ever to be able to come back as useful members of the staff. But this only accentuates the urgency of the situation. Some action is called for *now*.

We support wholeheartedly the General Medical Services Committee's repeated requests for more clinical assistantships.

But clinical assistantships are not enough.

To integrate the general medical service and the hospital service, the hospitals may have to be tolerant initially, and the practitioner himself must accept the idea of being part of the consultant's team. On the other hand, competence and skill in a specialty is still by no means incompatible with domiciliary medicine, and some general practitioners with the necessary time and experience will want to do responsible work. We believe this must be allowed them; for it is only the hope of being able to do responsible work in the hospital that will attract the right sort of practitioners into the hospital departments.

While there is obviously no intrinsic objection to practitioners assisting the hospital service by doing some emergency and " on call " duties, this should not be the prime objective in bringing them back into the hospitals. Indeed such work must bear a strictly fair relationship to the time spent in regular sessional work during the day.

We therefore suggest that a new hospital staffing structure for general practitioners is necessary. All hospitals should be able to offer a number of (1) *unpaid postgraduate training posts*. In the course of time doctors so employed should be able to apply for properly paid (2) *clinical assistantships* (as at present), and as such they would form part of the consultant's team. Finally, to give the necessary stimulus and incentive to doctors to take these posts, there should be some new grade such as (3) *general-practitioner specialist* to enable those with the necessary training and ability to do responsible work under the general direction of the consultant in charge of the department concerned.

At present the clinical-assistant grade is very vaguely defined in the Terms and Conditions of Service of the N.H.S. It has been differently interpreted in different places. In our view the term " clinical assistant " should apply only to practitioners working under the immediate supervision of a consultant, whereas the new grade of general-practitioner specialist should include those who do fully responsible work under the general direction of the consultant. This is, we think, a better title than that of " general-practitioner consultant ",[5] because we maintain with Fox [4] that the practitioner should remain a member of the consultant's team. In remote areas he may have to work almost entirely without supervision, but even in these rare circumstances a full consultant should be available for general direction and occasional consultation.

Both in equity and to prevent possible abuse, we suggest that clinical assistants should be paid at approximately the rates for senior hospital medical officers and general-practitioner specialists at approximately consultant rates.

RELATIONSHIP BETWEEN PRACTITIONERS

Partnerships

There has been a tendency recently to find fault with the partnership principle.[6] We attribute this to the notion that all partnerships pool their patients, so that patients never know whom they are going to see next—which is certainly an abuse of the partnership principle. But only in large groups is there really a danger of losing the personal doctor-patient relationship. In partnerships the patient should still choose his own doctor, and he can then change (within the group) with the minimum of bother

3. Fry, J. *ibid.* 1959, i, 124.
4. Fox, T. F. *Lancet*, 1960, i, 743.
5. Report of the General Medical Services Committee, 1960; paras. 54 and 55.
6. Hamilton, J. G. M. *Brit. med. J.* 1960, i, 23.

and embarrassment if this should be desirable owing to a clash of personality.

Where three to five doctors work together for mutual convenience, there are many potential advantages:

1. The pooling of resources, as in a central surgery, makes it possible, economically, to provide the very best equipment and premises together with secretarial and nursing help.

2. " Locums " or " assistants " become redundant.

3. A certain amount of " specialisation " within the group becomes a real possibility.

4. The mutual association is itself a great stimulus to improve standards.

5. The knowledge that there are other doctors interested in one's patients is a great relief from anxiety during absence, through illness and holidays.

6. A good firm " tradition " can be built up.

7. Time can be found for postgraduate study and for doing hospital sessional work without disrupting the twenty-four-hour round-the-clock 365-day service that the general public seem to take for granted.

8. All these advantages to the doctor have repercussions to the benefit of the patient.

Singlehanded practice may be necessary in certain restricted areas. Some doctors prefer it, and there should be room for such individualism. Where an unusually small list is geographically unavoidable, or for other local reasons expenses are unusually high, it seems only reasonable that such singlehanded doctors should receive any help necessary for carrying out their duties efficiently. Nonetheless we think that, provided they try to maintain the personal nature of their services, small groups of doctors who work together have the best chance of achieving the highest standard in family doctoring, especially when they have hospital appointments and good liaison with the local health services.

We think, therefore, that the Royal Commission was wrong to suggest that the financial incentive to partnerships was excessive (para. 342). In point of fact the only incentive was that two loading factors became payable if (for example) a doctor with a list of over 3000 patients should take in a partner. This meant that the partnership so formed received an additional £500 as compared with the singlehanded doctor. But, in view of the (nearly) doubled expenses, this seems to us inadequate justice rather than excessive incentive.

Assistants

Nor do we agree with the Royal Commission's views about assistants (para. 355). The general practitioner gives a personal service to patients who choose him. The doctor-patient relationship is the very essence of this service and there is really very little work that should be delegated to an assistant. (A qualified nurse is more useful.) The Royal Commission's comparison with solicitors and architects only illustrates the wrong thinking that has led to this paragraph. We believe that the only assistants allowed should be: (1) assistants with a view to partnership (any number of assistants being allowed up to a maximum period of, say, two years); and (2) trainee assistants.

The permanent assistant undermines the principle of the doctor-patient relationship, and suggests that an inferior and impersonal sort of general practice can exist. Special circumstances may justify the temporary employment of an assistant—e.g., the illness of a singlehanded principal—but permission to employ one should be strictly controlled.

An incidental benefit of the abolition of assistants would be an increase of the size of the Central Pool.

FAULTS RELATED TO METHODS OF REMUNERATION

The Capitation Fee

The capitation-fee method of payment has been widely criticised. It has been said that it promotes " head-hunting "; that it takes no account of the quality of work done, nor of the expenses involved in trying to provide good premises or expensive equipment; that it bears no relation to the age, experience, qualifications, or post-graduate study of the operator; and that the only way a doctor can get an above-average income is through an excessive list of patients.

These are at least theoretically valid criticisms; yet the Royal Commission (minority report para. 75) reported that they were told of no really satisfactory alternatives. A system of payment by fee for each service rendered probably has just as many faults. Unless the patient pays at least a substantial portion of the fee, such a system would not promote the particular sort of doctor-patient relationship so much prized in private practice. Indeed it really only amounts to an alternative way at counting the heads—and it would be very cumbersome and expensive to administer.

The capitation fee has moreover some real advantages. It removes the financial barrier between doctor and patient. The doctor's conscience is the sole guide to how often a patient should be visited; and we believe it is the best guide, always provided he has the time and facilities he needs. The patient has plenty of means of redress if he thinks he has not been adequately treated.

In short, we believe that the best prospects lie in trying to improve the capitation-fee system and in evolving ways in which its admitted faults can be alleviated.

Size of List

The argument about how many patients one doctor can look after satisfactorily will never cease, because there is no answer to it. But certain facts are incontrovertible:

1. There must be a minimum number below which a doctor cannot get enough experience on which to build up his knowledge and wisdom.

2. For each one of us, separately, there must be a maximum above which our treatment becomes hurried, if nothing worse. The point about the lower limit is that, where a doctor has a very small list, it seems wiser to encourage him to increase the number of his patients rather than to pay him more for doing so little. In other words, putting the loading on the capitation fee for patients between 500–1500 is a better incentive than loading the 1–1000 fee; for it encourages a minimum list of 1500.

In certain circumstances, it is said, an energetic doctor can look after as many as 3500 patients. But two facts are clear. First, if this is true, the particular circumstances which make it possible (e.g., the compactness of some urban areas) imply that longer working hours are not necessarily involved. If so, a system of payment in which the basic capitation fee remains the same up to any number is inequitable, and a good case can be made out for a diminishing capitation fee above a certain number. Secondly, some time for recreation and postgraduate study is essential if the quality of service is to be improved; and there can really be no question but that two doctors in partnership can provide a better service to 3500 patients than either of them can provide alone.

The Royal Commission wanted to keep a wide spread of incomes in general practice. But surely they were wrong in using this as an argument for retaining large lists (para. 344)? Fair distribution of the Central Pool seems to us an infinitely more important consideration. If, indeed, a wide spread of incomes is desirable, some way *must* be found whereby higher incomes can be achieved otherwise than by busting oneself trying to look after an excessive number of patients. Higher incomes should be possible when adequate lists are associated with experience and high standards of work.

Though we do not favour compulsory reduction of the maximum list, we think it would be fair to discourage them by making them less profitable. This could be done, for example, by reducing the capitation fee for patients over 2500 (perhaps on a sliding scale). The full fee would, however, be payable if an assistant with a view to partnership were employed.

The Loading Factor

One of the principles behind the loading factor is that the basic cost of running a practice does not rise in proportion to the size of the list. Even under the new improved scheme of distribution, the maximum loading amounts to only two-thirds of the average practice's expenses—so it certainly has not been increased excessively.

Differentials

The Royal Commission's figures show that the size of a practitioner's list is the greatest single determinant of income. The commission suggest (para. 342) that greater weight should be given to items other than capitation, and this deserves serious consideration. Special payments to meet special circumstances (e.g., mileage, inducement payments, initial practice allowances, and separate payment for midwifery services) will obviously have to continue. We believe that there are other possible differential payments. If it can be shown that these are fair and reasonable, the fact that they must be paid for out of the pool and consequently cause the general level of the capitation fee to fall, should not prevent their introduction. The following are possible examples:

Old age.—A contribution from the department of public health and social medicine of the University of Edinburgh [7] suggested that in general the practitioner and his patients grow older together. Consequently the more senior and experienced practitioner tends to have a greater number of old people on his list. But old people need more care and attention, and particularly more visitation at home, than the general average. It seems to us, therefore, that there is a very good case for loading the capitation fee for all patients on reaching, say, 65 years of age. Such a plan might prove troublesome to start administratively, but once started it should be fairly simple. (There may be a case to extend it to the first years of life. Indeed Elliott's proposals for distribution,[8] with a payment for experience and an optional scheme of loadings for the young and the old, is an admirable alternative.)

Special services.—The nature of general practice differs according to local circumstance. It would seem right that services over and above those *necessarily* provided by all practitioners should be separately paid for on an item-of-service basis—and that they should not be discouraged. This is already done for inoculation and vaccination and midwifery, but it might be extended to include minor operations, anæsthetics, and pathological investigations where hospital facilities are not immediately available.

7. *Brit. med. J.* 1959, ii, suppl. 119.
8. Elliott, W. A. *ibid.* 1960, i, suppl. 349.

Differential awards.—General practice remains the only branch of medicine in which no attempt has been made so far to reward either merit or experience. Since merit as such cannot be assessed, perhaps an experience award is about the only kind that will prove generally acceptable. We feel, however, that any award would have more meaning if some additional responsibility was implicit in the receipt of it.

An improved trainee scheme, such as that proposed here, would bring with it the responsibility of training and would do more to raise standards of practice than a simple experience award. However, either scheme would be better than none!

SUMMARY

1. The status of general practice must be raised before a rise in standards can be expected.

2. General practice must be better taught at the graduate level, and to this end an extension of the trainee scheme is suggested.

3. All practitioners should spend three years in hospital appointments before being accepted as principals in general practice.

4. Diagnostic facilities should be made available to all National Health Service practitioners forthwith.

5. Postgraduate education should be encouraged by every available means. Automatic payment of locumtenens fees to all doing accredited courses of over forty-eight hours, and more general-practitioner clinical assistantships, are suggested.

6. The need to bring domiciliary and hospital medicine together is stressed. To this end a career grade of general-practitioner specialist is proposed.

7. Partnerships should continue to be encouraged and permanent assistants should be permitted only in special circumstances and temporarily.

8. The financial inducements to specialism are excessive. Rates of pay for experienced and established practitioners should be upgraded in relation to those of consultants.

9. The distribution of the Central Pool should be modified with a view to encouraging good work. The following suggestions are made:

(*a*) The basic capitation fee should be reduced for patients in excess of 2500 (except where an assistant with view is employed). (*b*) The number of payments by item-of-service might be increased. (*c*) A scheme for differential payments to centrally selected general-practitioner trainers is put forward. (*d*) Ways of paying more for the care of the aged are suggested—perhaps by a loading factor on all patients over 65 years of age.

10. Where changes are necessary, desirable, or fair, the fact that the general level of the capitation fee would thereby be reduced should not be allowed to prevent their introduction.

"... dressers and clerks rightly show great loyalty to their own 'Firms'; none the less it should be stated once more that the practice of the whole of the hospital is open to all clinical students. The wise student soon finds out that he is welcome in departments other than those to which he is attached, providing he politely introduces himself and asks if he may attend to see how the different diagnostic and therapeutic procedures are carried out. Being a surgeon I may be inclining towards bias when I imagine that every student gains something from a glance at a human brain, heart, lung or the interior of a joint, when these have been displayed in the living subject; he should at least have seen the heart explored by a catheter and have seen the radiological procedures daily used to study the interior of viscera, tubes, vessels and cavities."—Prof. A. L. d'ABREU, *Queen's med. Mag.* February, 1961.

Conference

EVERYBODY'S BUSINESS

FROM A CORRESPONDENT

THE annual conference of the National Association for Mental Health was held at Church House, Westminster, on March 9 and 10.

Mental Hospitals of the Future

Opening the conference, the Minister of Health, Mr. ENOCH POWELL, called for bold planning of future hospital provision. The essential idea was to work out the pattern of hospitals required for the mid 1970s, based on an assessment of future demand. He believed that not more than half the present places for mental illness were then likely to be needed, representing a redundancy of 75,000 beds. This was a statistical projection, based on present trends and, with courage, we ought to pitch the estimate lower still.

These places ought to be mostly within general hospitals, rather than in great isolated institutions, though a small minority of patients would still require security. The change implied the elimination of the greater part of our present mental hospitals—a colossal undertaking, particularly in the sheer inertia of mind and matter to be overcome. In spite of the physical solidity of the buildings, there was no appropriate future use for the great majority, and he would resist any attempt to foist another purpose on them, unless such a building was required in such a place for that purpose.

Mr. Powell said we must strive to alter our whole mentality about hospitals, and especially about mental hospitals. A hospital was a shell to contain certain processes; and when the processes changed, the shell must most probably be scrapped. The improvement of existing facilities might militate against their supersession by something different and better. However, hundreds of men and women had given years to the service of mental hospitals, through years of scarcity and neglect, and it demanded no mean moral effort from them to recognise that the institutions were doomed. The transformation required was not only that of buildings, but of a whole branch of medicine, of nursing, and of hospital administration.

For the subnormal, the prospects for change seemed far less dramatic, and numbers were likely to increase. But we should not passively accept a corresponding increase in hospital places or the perpetuation of the present hospital pattern. It would, though, be quite unrealistic to state intentions for hospital provision without working out community care in equal detail. The hospital plan made no sense unless doctors outside accepted greater responsibility and were supported by new development of local authority services. Local health authorities were therefore to be called on to map out their joint future with that of the hospitals. Local authority services should be able to cater for a whole gamut of different degrees of need, between the complete independence of full health and the need for care and attention, little short of that provided by a hospital.

The Minister doubted whether finance was now the limiting factor; this year, the capital expenditure of local health authorities had been half that of hospital capital expenditure. He believed that a much clearer statement was required of the provision at which local authorities were aiming. Only the consciousness of a great and expanding task, and of a great service destined to develop, would secure the flow of personnel into community care, but, in 1961, it was intended to erect the scaffolding of a professional training for the social worker.

Integration

Prof. A. V. NEALE said that, following usual British practice, the mental health services had evolved through stages of "adhocery". The ten-year interval between the National Health Service Act and the Mental Health Act had been a useful incubation period. He was the first of many speakers to refer to medical education and to the fact that diseases of the mind and of the body have been kept in separate compartments in teaching. Progress in medicine depended on interaction with cultural attitudes, and mental-health centres might play a part in education of the community.

In the discussion, Dr. RUSSELL BARTON asked whether education and training in the next 15 years could sufficiently make up for the inadequate role of the teaching hospital, which was producing the "incomplete physician", lacking a barn-door knowledge of psychiatry.

Dr. D. H. CLARK said that the revolution in British psychiatry had come in and from the mental hospitals, which have led the world in their development. He asked whether upgrading was to continue and whether the Minister was aware of the squalid conditions in which many patients are still housed.

Treatment in Hospital

Dr. WILLIAM SARGANT said that the recent development of physical methods of treatment would allow a reconciliation of general medicine and psychiatry and that there was no point in persistently trying to emphasise the differences between the two. Most types of patients now being admitted to mental hospitals could be treated at least as well in general hospitals. At St. Thomas's Hospital, psychiatric outpatient attendances now numbered 17,000 per annum, and the inpatient unit of 20 beds admitted up to 177 patients in the year, with an average stay of 6 weeks. Most outpatient attendances were for treatment, and he particularly emphasised the value of outpatient E.C.T., which should be available in all areas. If medical staff divided their time between mental and general hospitals, there was no need for a split between the two; and some competition was important between different treatment facilities in the same areas. Since new treatments were likely to be chemical or physical in the main, he thought they were best developed in general hospitals.

Dr. STANLEY SMITH said he would attempt to answer the question whether mental hospitals were now an anachronism. In the Manchester region, 11 general-hospital psychiatric units had been set up which, with cooperation from the geriatric services, could adequately look after a population of a quarter of a million each, using about 120 beds. In 1958, only 32 patients had gone to mental hospitals from Oldham and Burnley, with a combined population of half a million. However, some of the consultants felt that about 5% of their admissions would require to be transferred to mental hospitals. Because of the fall in numbers of patients resident at Lancaster Moor mental hospital, resulting from these developments, it was decided that the accommodation, nursing staff, and ancillary services should be used to the full, by catering for definite needs in the community. Within the mental hospital, a comprehensive hospital was being created containing a psychiatric admission unit, long-stay annexes, geriatric and chronic sick accommodation, a unit for subnormals, and others for neurosurgery, ophthalmic cases, orthopædics, and transfusion services. The geriatric patients were being largely cared for by general-practitioner clinical assistants.

Dr. W. A. HEATON-WARD said that the types of subnormal patients likely to require hospital care in future were, firstly, young children with suspected subnormality, and, secondly, adolescents and young adults whose subnormality was accompanied by disturbed behaviour. The second type, with I.Q.s of 70 to 90, required separate units, distinct from those for the severely subnormal, and often needed prolonged treatment.

Most hospital treatment was concerned with the accompaniments of subnormality, rather than the basic condition, and was inseparable from training. It had been revolutionised in recent years by the phenothiazine drugs and by the development of occupational and industrial therapy. Progress was impeded, however, by the level of medical staffing, which averaged 1 consultant to 700 patients, and in some regions consultants were responsible for more than twice this number, as well as for outpatient services. Other branches of medicine needed to be convinced that the care of the subnormal had progressed from a purely custodial approach to an actively therapeutic one. This was no time for take-over bids from pædiatrics, but for cooperation between the two specialties.

Community Care: Fact or Fiction?

Prof. R. M. TITMUSS said the English tended to express aspirations in idealistic terms, but public opinion might then be confused into thinking these had become reality. Beyond a few brave ventures, there was little evidence of attempts to hammer out the practice, as distinct from the theory, of community care, though institutional policies assumed that someone knew what it meant. The trend was supported by awareness of the disabling effects of institutional life and of the virtues of the normal social environment. But we must examine its meaning at the level of concrete reality—for instance, the large deductions made from the earnings of patients undergoing industrial and social rehabilitation

If community care was to be a reality, it must start in the hospital and encompass all the social services. To scatter the mentally ill in the community without adequate provision was not a solution, even financially, since it would involve more expenditure on police, unemployment benefit, drugs, &c. Ten years ago, the Mackintosh report had pointed to the acute shortage of social workers in the mental-health services. Since then, psychiatric social workers employed by local health authorities had been increased at the rate of only 2·25 per year (from 8 to 26). Allowing for price changes, increased population, and the increased number of the mentally ill in the community, requiring treatment, local authorities were probably spending a smaller amount per head on community services for the mentally ill than in 1951.

The proposed reduction in mental-hospital beds implied a remarkable degree of optimism about the rapidly rising readmission-rate and about the parts to be played by general practitioners and local health authorities. As an assurance that we meant business, Professor Titmuss suggested a specific grant to local authorities for community services of £10 million in 1961–62; the establishment of 15 courses for social workers by 1962, with grants for students; and a Royal Commission on the recruitment and training of doctors, with special reference to psychiatry. He felt we were drifting into a situation in which care of the mentally ill was being transferred from trained staff to untrained or ill-equipped staff or no staff at all.

Dr. P. A. TYSER said that local authorities must continue to develop all their preventive services, since they all had a bearing on mental health; early ascertainment and treatment and social support could prevent individual and family breakdown. However, the different financial arrangements of hospitals and local authorities meant that difficulties occurred over the division of responsibility.

Variations between local authorities made it impossible for all to follow a single plan, and some would find it impossible to fulfil all their obligations under the Mental Health Act at an early date. Some services might be uneconomic for certain single authorities and might have to be discussed with their neighbours; they would also have to be related to the hospital facilities available. Trained staff was the first priority, and it was useless to plan buildings without first ensuring that staff would be available when they were completed. The use of the halfway hostel depended very much on the character of the local psychiatric hospital; experience at Winston House, Cambridge, indicated that with an active hospital, organised on modern lines, the demand was not likely to be great. He did not feel that hostels for long-stay patients, working irregularly, were a priority. Although long-stay accommodation would have to be provided for the elderly mentally ill, the day centre was a more immediate priority, relieving both hospitals and part-III accommodation. For the subnormal, a junior training-centre was the first priority and should include a hostel. Similar facilities for adults should then follow.

Mr. M. A. GILLESPIE, a local-authority psychiatric social worker, referred to the need for free communication between "field workers" and administrators in the service. Mental-welfare officers were now social workers as well as statutory officers; their work could be divided into acute short-term cases; cases requiring support over a limited period; and those which went on indefinitely (often the subnormal). If local health authorities were to establish a community care service, there was an urgent need to provide training for those doing social work, even though it was not easy to establish the advantages of training in concrete terms. In addition to increasing staff, there was a need to make more efficient use of existing resources. It might be many years before the effectiveness of community care could be judged, and it would be fatally easy for the pendulum of opinion to swing back to institutional care.

Public Attitudes

This session consisted of three recorded conversations, illustrating attitudes to mental illness, which were commented on by a panel of speakers. Miss MARY GRIEVE said that "Everybody's Business" was a declaration of hope, rather than a fact, since many people preferred to evade such questions, which aroused shame and fear, rather than come to terms with them. A recent article on the subject in *Woman*, which has a readership of 10 million, produced only 14 letters in reply. Dr. J. P. HORDER said that it was difficult to believe that a general practitioner with a full list had the time to deal with psychiatric problems adequately. For students, the attitude of their teachers was more important than the time devoted to the subject, and psychiatry might therefore best be learnt in the post-graduate period. He felt that hospitals should make sure that the general practitioner did not lose interest in his patients during their hospital treatment, by keeping him informed of what was happening. Mr. KENNETH ROBINSON, M.P., said that the public attitude was very different from 10 years ago, but there had not been a comparable change in medical opinion. It would be disastrous if staff of any type were segregated into purely acute or chronic hospitals, and this should be avoided by rotation. The Rev. G. R. DUNSTAN said that mental-health workers should establish their position with the public by helping to deal with the normal anxieties of child-rearing; they would then become acceptable in the context of mental illness.

• • •

The conference was dominated by the Minister's announcement of policy on the future of mental hospitals, which aroused not only admiration for its boldness, but also profound anxieties about the future of their staffs, particularly trained nursing staff. Many speakers called for assurances that this reservoir of skill and experience would not be wasted, more especially as there seemed little evidence at present of any alternative body of trained workers to operate in the community. There was also anxiety about whether the improvement of existing hospitals might come to an end. Professor Titmuss's devastating analysis, which indicated that community care seemed more fiction than fact at present, received some support, though many felt that the ideals of community treatment should not be lost sight of. An unexpected though persistent topic was the need to improve the place of psychiatry in medical education; and this was part of the generally acknowledged demand for the spread of information on mental health throughout society, both professional and lay.

Medicine and the Law

A Departure from Recognised Practice

A PSYCHIATRIST undertook early in 1949 the treatment of an intelligent middle-aged woman in an anxiety state.

For some months she saw him in his consulting-room and wrote to him copiously as part of the therapeutic process, giving or sending him the letters, which he later returned to her and which she preserved. She developed towards him deep feelings of love, obsession, and bondage, which he explained to her as being part of the process of transference, and he advised her to continue the treatment as she had a good prospect of recovery. After six months she was better in health, but felt herself to be deeply in love with him and was convinced that he was not indifferent to her. It was decided that the sessions should cease; but the doctor, taking the view that a sudden withdrawal might cause a relapse, decided on a series of friendly and innocent social contacts with her, involving meals in restaurants and taxi journeys, a single visit to her home, and, the trial judge found, conversations about a holiday or weekends together; but the doctor gradually withdrew from the relationship, and the woman, by then emotionally aroused and distressed, attempted suicide at his home. He thereupon resumed the psychotherapeutic treatment in a final attempt to resolve the transference, but brought it to an end as it was proving of no avail. The woman's mental condition deteriorated to such a degree that she became wholly incapable of work.

She decided on proceedings against the doctor, alleging that her illness was caused by his wilful misconduct (including gross sexual misconduct) and professional negligence, but for various reasons those proceedings were delayed for 10 years. The doctor denied the allegations.

Mr. Justice BARRY said that in the first phase of treatment there was nothing improper or unprofessional in the doctor's conduct, and his Lordship entirely absolved him from any charge of misconduct of a sexual kind; but the decision to embark on social contacts which involved being alone with this patient, whatever the motive might be, had to be judged in the light of the medical evidence as to the duties and obligations of a psychiatrist dealing with a patient.

A psychotherapist must exercise the very greatest care when delving into the dark secrets of the human mind and explosive emotional forces, for if mistakes were made in psychotherapy or analyses which employed the technique of transference the consequences might be disastrous. It was most important to adhere to the highest standards of treatment within the existing state of knowledge of the profession. The doctor here had agreed that in originating the technique of social contact with this patient he was departing from the standard practice in this special branch of medicine, but said that it was justified by the exceptional circumstances of this case. His Lordship, however, had considered the evidence of the distinguished practitioners in this branch of medicine who had all spoken with one voice on this subject, and he accepted without hesitation the evidence of Dr. Stafford-Clark that there could be no separation in this kind of case between social and professional contacts, that it was an exacting form of treatment, and that a doctor was put into such great difficulties if he had any social contacts with his patients that if they became unavoidable a doctor should withdraw from the case. It followed that talk of holidays with a patient, even though not seriously intended and actuated by kindness, and frequent social meetings or gestures of affection, would be utterly disastrous for a patient undergoing this kind of treatment, a patient who had already declared her passion for the doctor concerned and was highly sexed. In such circumstances such social contacts would cease to be treatment and would become appalling complications, for they could only be misunderstood by a patient in the condition of this lady.

His Lordship fully realised the dangers to doctors in this branch of the profession, and so did this doctor. But his Lordship was forced to conclude that with the best intentions in the world he had made a tragic mistake; and there had been here a departure from the recognised standard, which had resulted in gross deterioration in the patient's health. On the evidence which his Lordship preferred it would also amount to negligence in treatment. His Lordship was not laying down as law that no psychiatrist could in any case take a patient out; that would be ridiculous. But having regard to the nature of this patient his Lordship was not satisfied that there was any body of opinion which would have thought it desirable to bring this highly sexed, highly emotional woman, already deeply in love with her doctor, into intercourse of the kind that occurred here. Negligence of that kind had been established and there must be judgment for the plaintiff for £6000 damages. A stay of execution on terms, pending consideration of an appeal, would be granted.

Landau *v.* Werner.—*Queen's Bench Division:* Barry, *J.* March 7, 1961. Counsel and solicitors: G. R. F. Morris, Q.C., and James Dunlop (C. M. Beck & Co.); Norman Richards, Q.C., and John Spokes (Le Brasseur and Oakley).

M. M. HILL
Barrister-at-Law.

No Doctrine of Diminished Responsibility in Matrimonial Cases

A wife petitioned for divorce on the ground of the husband's cruelty. The husband denied the charge.

Medical evidence established that in 1937 the husband sustained a head injury, followed by loss of memory for about five months. Later, his condition improved, but he continued to suffer from depression and irritability, being liable to outbursts of hysteria, and was irresponsible in some ways. By 1948, when the marriage took place, the husband, though not fully recovered, was well enough to undertake the ordinary duties of marriage. In 1955, he fell in his bathroom and, in falling, injured his head in the area of the previous injury. Thereafter he suffered from loss of memory, headaches, lassitude, and loss of powers of concentration, and became so irresponsible in business matters that in 1957, on medical advice, he retired and his affairs were thereafter managed by someone else, who was given a power of attorney.

Mr. Justice KARMINSKI said that there was no suggestion that the husband's mental condition was at any time such as to amount to insanity within the McNaughten rules. Had that plea been established, there was no doubt that the charge of cruelty must have failed. Counsel for the husband had advanced the novel argument that there might be a half-way house between full legal responsibility and that immunity from legal responsibility which insanity within the McNaughten rules conferred, on an analogy with the doctrine of diminished responsibility introduced into the law by section 2 of the Homicide Act 1957. That doctrine, however, applied only to homicide cases. The matrimonial law knew no doctrine analogous to it. The husband's treatment of the wife, taken as a whole, and having regard to its effect on her health, amounted to legal cruelty and she was entitled to a decree *nisi*.

Graham *v.* Graham—*Probate, Divorce and Admiralty Division:* Karminski, *J.* March 2, 1961. Counsel and solicitors: Cyril Harvey, Q.C., and Guy Seward (Wrentmore & Son, for A. E. Hamlin, Sheringham); J. B. Latey, Q.C., and J. Elson Rees (Lee Ockerby, Johnson & Co.).

D. R. ELLISON
Barrister-at-Law.

In England Now

A Running Commentary by Peripatetic Correspondents

"WHERE are you going?" I asked my young relations. "We haven't a clue," was the answer. "We shall chuck a couple of suitcases into the boot, stick the A.A. book on the seat between us, and just go."

So, with my pen and a blank sheet of paper on the desk, do I feel. A voyage into the unknown? Navigation? By guess and by God? Yes, and something else. To get the thing in perspective there must be a brief biographical note. A couple of years ago I became a grandfather, and with that event came a subtle realisation of the joy of growing old and an appreciation of those words from *Ecclesiastes*, "Children's children are the crown of old age."

When the Press, radio, and television are overcrowded with reports, domestic and overseas, indicating anger, clamour, malice, violence, and all manner of uncharitableness, a mood of gloom and despondency is easily induced. The interference is so great that the still small voice of calm is in danger of being stilled indeed. A neighbour of mine—a middle-aged man—is going about his lawful occasions in full possession of himself. Three years ago he was very ill. Five-and-twenty years ago his disease had 100% mortality. He and countless others, at home and abroad, are living monuments to the progress of medicine. The League of Nations failed as a political body, the United Nations may be on the brink of the same failure. But is there no health in the World Health Organisation? A friend recently journeyed, by invitation, to Moscow to operate on an unknown Soviet citizen; for in truth disease recognises no international boundaries nor iron curtains. When one considers the enormous benefits which modern medicine, not least from British practice, has conferred on men, women, and children, is it completely vain to hope that here is a pattern from which *Welt Politik* might learn something to the advantage of mankind? *Homo sapiens* forsooth.

• • •

Oakshott Mansion,
Little Oakshott,
Kent.

Dear Muriel,

How nice to hear from you and to get all your news. I do wish I was with you in Cannes!

Here in Oakshott things are much as usual with little news to report. Our only excitement has been Nannie—we still call her Nannie, though since the children grew up she's been more of a general stay and prop. Well, she went off sick for three months—think of it, three months!—and it turns out she had tuberculosis really. I didn't think *anyone* got T.B. nowadays. I mean it was all right for Keats and Mimi (or do I mean Fanny?) but I understood it just didn't *happen* any more.

You remember the dance we used to have in aid of the Sanatorium—such a good dance. Well apparently they have closed it down, the Sanatorium not the dance, for lack of patients, so now we have to give the proceeds to the Society for the Preservation of Rural England.

Well, anyway, Nannie had T.B. and a little man came round to see Henry and me, asking all sorts of questions. I mean he was quite a *nice* little man and I'm sure he was only doing his job, but really he was quite officious and Henry had to be positively *rude* to him in the end to get him to go away. He wanted us to go to the local hospital—for an X-ray he said—but you know what that place is like. You spend hours sitting in a place like an Undergound station, and although one doesn't quite like to say so, the people do *smell* rather.

Anyway, Nannie is back now, although still taking medicines. They make her terribly sick but, having no imagination, she just kept stolidly taking them until Henry suggested that it was doing her more harm than good. She was reluctant to believe this but I'm glad to say that British compromise won the day—she now takes a quarter of the dose and isn't sick. Thank goodness we can manage these things sensibly in this country. Not like the French!

I was glad to hear that you and the children were well. Poor Henry has had a nasty cough for weeks now, and I have been feeling terribly run down. It must be our age, and the climate. Still, Christmas is coming and we will have all the family round us—including the two babies I haven't seen before. It is a mixed blessing though, Christmas, since one has to visit the OAP's and the "wounded of two wars", and the orphanage, and all those other places. I suppose it does do *some* good though.

Well, a happy Christmas my dear.

Vera.

P.S.—There has been a sheep born in William's farm with five legs. They say it's all due to X rays and things so I'm *so* glad that Henry didn't give in to the little man and let me get X-rayed.

• • •

We made history in a small way by securing permission from London University to hold the B.D.S. finals in medicine at Harley Street. The restlessness normally engendered by a blazing June day was not mitigated by a seemingly endless procession of monotonously competent candidates. Searching for inspiration, the uninhibited song of the housekeeper's budgerigars prompted us to inquire after diseases which might be caught from birds. We did not expect, nor did we receive, enlightenment on the subject of psittacosis, and soon reverted to discussion of bleeders, fits in the chair, irregularities of pulse, and lung abscess. Everyone got through, but our secretary relayed some of the indignant remarks on ornithoses from the waiting-room.

Six months later dark December found us again devoid of new ideas on the fourth day. Straining our ears, we thought we heard a plaintive avian note from the basement. The candidate was ready for us, and in response to our invitation explained how silicosis, a lung disease, might be contracted by the repeated inhalation of sand particles scratched up into the face by infuriated birds who resented the daily cleaning of the floor of their cage. For a moment it was June and the sun shone again before we reverted to discussion of bleeders . . .

• • •

The smell started in the waiting-room during the summer. My builder opened the meter-cupboard and shut it hastily. "Dead rats," he said laconically. Some days it was there, and sometimes it went for days. This seemed to indicate impending plague or a faulty diagnosis. The smell seemed worse after a few dry days, so the nuisance value was small while summer lasted. Just before Christmas however, the smell changed and smelt like coal-gas. The gas board men were called in. "No coal-gas," they said, giving me a demonstration with the test paper; "you had better get the sanitary inspector."

"Sewers," he said. Nothing could have been more Spartan. He consulted with the builder on where to dig, so that when 'flu started to fill my waiting-room there was a large pit reaching nearly to the door. Anyone over 10 st. was in danger of being buried without benefit of my opinion. The moment of climax arrived when the man with the smoke tester arrived and fixed up his apparatus down the manhole in the backyard. Eagerly we pressed forward to the edge of the hole, as the smoke billowed out and emptied the waiting-room of patients, again without benefit of my opinion.

It was clearly coming from a bad join in the pipe that led off the drain to the vent. "That's luck for you," said the inspector. "All that needs doing is to remove the vent pipe and seal the draining." In a few minutes the manœuvre was completed and the hole closed with concrete.

The only thing is that when I went to surgery this morning the smell is still there. But I did want to get this down before seeing the psychiatrist tomorow.

• • •

To many of the human race
'Twould seem a sound idea
To rocket boffins into space
And keep the chimps down here.

Letters to the Editor

POLIOMYELITIS VACCINES

SIR,—The annotation of March 11 mentioned the fact that vacuolating virus had been found in many batches of attenuated vaccine. It failed to mention that no tests for vacuolating virus were done on any batches of killed vaccine up to 1961. Moreover, experiments at one of these laboratories (W.R.L.) show that this virus is resistant to formaldehyde. The rate of inactivation is such that one can predict that traces of the virus would be present at the end of the routine Salk process if the initial virus titre is in the region of 10^6, a fairly common finding in rhesus-monkey-kidney cultures. It was therefore not surprising that a proportion of individuals who had received Salk vaccine in this country was found to have antibodies to vacuolating virus. 13 out of 20 children's post-vaccination sera had antibody titres of more than 8. There is, therefore, a body of evidence that killed poliomyelitis vaccine in the past has contained vacuolating virus, probably in the living state. This alarming conclusion is somewhat mitigated by two facts. First, field evidence indicates that, so far, the virus has done the recipients no apparent harm; and second, future batches of vaccine must also pass a test for vacuolating virus. How easy it is going to be to produce killed vaccine conforming to the new standard remains to be seen. In the meantime, vaccine currently in general use consists largely of material on which tests for vacuolating virus have not been done because its existence had not been reported at the time of manufacture.

On the other hand, attenuated vaccine is given orally, and it now appears that the alimentary tract is refractory to the vacuolating virus. We have found no evidence of antibody formation in 32 children after repeated feedings of Sabin's original vaccines (known to contain at least 10^4 T.C.D. of vacuolating virus). Sabin also reports failure to recover the virus from the fæces of children fed the same vaccines. Thus, it apparently neither multiplies locally nor penetrates to other tissues.

Moreover, experience with the manufacture of the attenuated vaccine at the Wellcome Research Laboratories has shown that secondary seed batches can be prepared free of vacuolating virus directly from Sabin's original vaccines. The problem of vacuolating virus has in fact been solved for attenuated vaccine, as one hopes it soon will be for killed vaccine.

One is left with the suspicion that vacuolating virus will not be the last agent to be discovered lurking "hitherto undetected" in monkey-kidney tissue-culture preparations. In this respect the attenuated vaccine seems to have two advantages over the killed. First, it is produced under much more rigorous standards of animal quarantine and tissue-culture control, which reduce the chances of extraneous virus contamination. Second, the oral route uses the alimentary tract as a selective screen, as in the case of vacuolating virus, while subcutaneous injection carries the certainty of introducing directly into the tissue whatever is in the syringe.

The last sentence of your annotation could in fact be rewritten "What little we know about tumour viruses suggests that it is unwise to use a possibly virus-contaminated vaccine by injection when there is an oral alternative."

Wellcome Research Laboratories, Beckenham, Kent. ALAN P. GOFFE.

Public Health Laboratory, Newcastle upon Tyne. JAMES HALE
P. S. GARDNER.

CARE OF THE INJURED

SIR,—Since I write this letter from a very old and outdated hospital, will Mr. Qvist (March 4) please cross my name off his list of "the Clores and the Cottons of Accident Surgery", neither of whom would work in such surroundings?

What really disturbs me is his apparent complacency and doubt about the need for any change in organising our hospitals to care better for the injured.

In 1939, an interdepartmental committee criticised "the delays in many cases of serious injuries in commencing treatment . . . pointing to serious defects in the arrangements under which these patients are treated in a large number of our hospitals". In that year I was responsible for the emergency surgery of a very large general hospital, including the care of large numbers of major injuries. The seriously injured had to take their turn with other medical and surgical conditions in using all the hospital's services, and somehow be fitted into fixed and often very long operating lists. Under such conditions—and they still exist in most hospitals—delays in treatment are inevitable.

Following the interdepartmental committee's report, even preceding it, many memoranda from distinguished associations and papers from experienced surgeons have continually advocated the urgent need for reorganisation of our hospital accident services. Mr. Qvist's outlook seems to be in line with the decision of the authorities to do nothing.

Yet from recent surveys in Birmingham, Oxford, and Sheffield, it appears that 10% of the population each year seek hospital treatment for accidents. This is an enormous hospital-treatment load that must continue to be spread between general practitioners staffing the cottage hospitals and all interested surgical staff of larger hospitals, *according to the facilities that are now or can in the future be made available to them.* But this organisation alone cannot meet the criticism of the interdepartmental committee. The problems are well known. Prognosis after serious injury is directly related to the time in hours from the accident to the completion of plenary surgery. Severe and multiple injuries typical of present-day road accidents, and mostly sustained after 10 p.m., require much more than "operating units". Resuscitation and diagnosis require a high degree of laboratory and diagnostic skill, and facilities available immediately the patient is admitted, often to be immediately followed by lengthy surgical repairs calling for a high level of ability in anæsthetist and surgeon alike. General hospitals, with their prearranged operating lists, and their staff commuting between several hospitals to meet their many responsibilities, cannot *always* meet the additional responsibilities to the injured without very considerable delays, and the help of very junior and untrained resident staff. Hence the need for Mr. Qvist's "emporia". Like much else in his letter, this term is unnecessary in any constructive approach to the solution of the major medicosocial problem of this century.

If British surgery is to keep pace with surgical developments in other countries, new central accident units must be provided for each million or two of our population. There is no threat in this development of a "take-over bid".

The functions of a self-contained central accident unit attached to a large general hospital—and preferably a teaching hospital—can be defined as follows:

(1) It stands behind the accident services of its peripheral hospitals when they cannot meet their commitments, as well as providing the accident services for the immediately surrounding population.
(2) Laboratory, clinical, and specialist services on a 24-hour basis are complete in every detail.
(3) It has sufficient staff, of all grades, so that none is on continuous duty for longer periods than 12 hours in each 24.
(4) It is responsible for undergraduate and postgraduate training in accident surgery.
(5) It coordinates and develops the accident services of its region, and the teaching and training of ancillary medical personnel, with particular attention to first-aid.

In short it is the headquarters from which a closely coordinated regional accident service could be developed.

During its 20 years' life, this hospital has met most of these requirements, not by any directional edict, but by common demand. It could meet all of them if it was housed in an adequate building alongside a large general hospital.

Mr. Qvist is wrong in stating that the 24-hour service of the Birmingham Accident Hospital has broken down because of a shortage of radiographers. This shortage placed—and is still responsible for—an unnecessary extra strain on clinical staff.

His point that the time-interval between the accident and the completion of plenary surgery will be longer if the patient is transported to a large organised unit, than if taken to the nearest hospital, is debatable. If Mr. Qvist makes a study of this time-interval in a significant number of injuries such as compound fractures, head, thoracic, abdominal injuries, and burns, from his hospitals, I will do the same for a similar number of like injuries transported to us from peripheral hospitals. I would be prepared to wager a small sum on the result.

Birmingham Accident Hospital,
Birmingham, 15. WILLIAM GISSANE.

SHORTAGE OF HOSPITAL STAFF

SIR,—While we would agree with the views of Miss Darnell (March 4), that good and informed publicity is essential for recruiting nursing staff, this is one facet of the problem of shortage of nurses.

There is a waiting-list of candidates to train in the teaching hospitals, but it is quite otherwise in the non-teaching hospitals. In our experience mental hospitals have extreme difficulty in attracting candidates, even though they are prepared to accept those below the recommended educational standards, and overseas candidates with a minimal knowledge of English. The wastage-rate is disproportionately high, the more promising candidates often leaving first. This has led to a vicious spiral, which will not easily be broken.

We consider that it is not sufficiently well recognised that in the average mental hospital the following practices are common:

(1) A ward of 50 patients with only one nurse, who may not be fully trained.

(2) A " disturbed " or admission ward of up to 30 patients (including suicidal patients) staffed by one trained nurse and two student nurses. This degree of understaffing can lead to potentially dangerous situations, and incidents which can be frightening for new members of the staff.

(3) Two nurses on night duty in a geriatric ward of 50 patients, where many patients are incontinent, some doubly so, and many are liable to become restless or confused.

(4) No proper arrangements, due to shortages, to relieve nurses during mealtimes, or absences when escorting patients elsewhere; in these circumstances one nurse " covers " 2 or 3 wards. This applies also when staff are away on leave or sick.

(5) Under these conditions nurses are unable to get to know more than a few patients individually, and the time-consuming but rewarding work of rehabilitation of chronic patients must be sacrificed to maintaining minimum standards of care. The ideal of treating patients in small groups is rarely achieved.

The situation is less desperate in non-teaching general hospitals, but the basic problems are similar. As soon as there are too few nurses to do the work adequately, new recruits are rapidly lost. They are overwhelmed, partly by the physical effort of trying to do the work of two, and partly, because youth is idealistic, by the impossibility of doing a satisfactory job. The nurses with whom we have discussed these problems feel that the points we have made are more important than the inconvenient hours and comparatively poor pay.

We have worked in several large mental hospitals in the London area; these problems are common to all. As we do not wish to identify specific hospitals, may we sign ourselves

TWO SENIOR REGISTRARS.

SURGEON AND ENGINEER

SIR,—Your annotation of Feb. 11 and ensuing letters overlook some of the current work in this field.

For instance, the research department of the Limb Fitting Centre, Queen Mary's Hospital, Roehampton, has had an engineer working full time with a doctor for four years. At the Institute of Orthopædics Poliomyelitis Centre, we have received a large grant from the National Fund for Research into Poliomyelitis and other Crippling Diseases through the Committee for Research into Apparatus for the Disabled, whose chairman is Sir Harry Platt. With this money we have over the past two years employed a senior consulting engineer working maximum part-time ($^9/_{11}$ths) and a qualified engineer/draughtsman working full time. Workshop and secretarial staff are provided jointly by the C.R.A.D. moneys and the Medical Research Council. As part of our programme, we are cooperating very closely with Roehampton on the development of motors for moving flail arms and for arm prostheses.

But there is a point which has not yet been taken up by your correspondents—namely, that it is essential for the engineer and the doctor concerned with any project first to spend some time integrating their points of view; the doctor must learn about engineering and the engineer must learn some biology. Without this development of a joint viewpoint, which is the practice of true biological engineering, no experimental project can be developed to a stage where it becomes the synthesis of all the relevant factors—anatomical, physiological, clinical, and engineering. There are usually many ways in which a certain machine can be designed, but there are likely to be very few ways in which such a machine for use with the body can be designed to produce the most efficient and effective results. Often the way chosen is not the way that the engineer without any knowledge of biology would prefer to design the apparatus; the engineer who really understands what he is trying to do in anatomical and physiological as well as engineering terms will be able to see that the design which is finally chosen is the one which presents the best compromise of all the relevant factors. It is my belief that no doctor without a proper engineering training can really even suggest as good a method of designing apparatus as can a proper design engineer who understands the clinical factors. The latter cannot, of course, understand them completely, nor can the doctor understand the relevant engineering factors completely, but if each will work hand in glove with the other results will be obtained which are well worth the effort.

I agree with Dr. Scales (Feb. 25) that competition is essential, but since some workers have met with lack of understanding of the nature of their problems, it is valuable to know that at least one committee (C.R.A.D.) exists able to encourage work in this field.

There is, however, also a need for an organisation which would provide library facilities, would keep research-workers in touch, and would do some research on its own. I am not so convinced that a testing service for appliances is really practical at this stage in the profession's knowledge of biological engineering. Nevertheless, that may come in time. I think it would help a great deal if the Biological Engineering Society could be given the support of as many interested official bodies as possible so that in time as the subject grows it will be able to provide these facilities for its members.

Institute of Orthopædics
Poliomyelitis Centre,
West Hendon Hospital,
London, N.W.9. A. B. KINNIER WILSON.

SIR,—Mr. Charnley complained in his letter (Feb. 25) that engineers fail to cooperate positively with surgeons.

My own experience does not support this statement.

During the past few years I have been given all the assistance for which I have asked by the Faculty of Engineering, King's College, London. For instance, I was helped with:

(1) The design of an implant to replace the hip, neck, and upper third of the femur.

(2) The theoretical and experimental determination of the forces acting on the hip.
(3) An investigation into the mechanism of fractures of the neck of the femur.[1]
(4) The design of a new sliding pin for the internal fixation of femur-neck fractures.
(5) The testing of the mechanical strength of a certain bone-gluing agent.

This help was given generously and enthusiastically, and it is a pleasure to record my sincere thanks to all concerned.

Lewisham Hospital,
London, S.E.13. A. C. BINGOLD.

ÆTIOLOGY OF COARCTATION OF THE AORTA

SIR,—The admirable article on this subject by Dr. Campbell and Professor Polani (March 4) makes me think of the numberless abnormalities great or small which may be associated with this or other diseases. All may cause trouble to ordinary individuals before their nature is properly understood.

Personally, like most other boys at school, I learned to catch a cricket ball fairly well, although it might cause me considerable pain, but I could not throw it to the wicketkeeper quickly enough, especially if I was fielding at a good distance. It was a considerable time before I discovered that the construction of my right shoulder-joint was somehow at fault. In fact it seemed to work rather like a girl's shoulder joint and I could not overcome the difficulty.

I write this to emphasise the importance of rightly recognising the nature of a difficulty, even if it cannot be perfectly overcome.

London, N.W.1. F. PARKES WEBER.

RECOVERY ROOMS

SIR,—Dr. Buxton Hopkin (Feb. 4) is to be commended for bringing the subject of recovery rooms to the fore at this time; most British anæsthetists who have had experience of them must surely agree on the invaluable contribution they can make to the welfare of the patient in the immediate postoperative period. It is to be hoped that adequately designed and staffed recovery rooms will be included in all new hospitals, and that economic or other obstacles will not hinder the provision of such facilities throughout the country as soon as possible.

The detailed design of these rooms will, as Dr. Buxton Hopkin indicates, depend to a great extent on local conditions, and the likely problems are discussed at length in at least one book.[2] There are, however, a few points which call for comment in the light of our experience here.

The main recovery room at The Presbyterian Hospital is a 15-bedded unit serving 14 operating-theatres, and enables the average daily load of about 40 patients to be handled easily and efficiently. All non-infected postoperative patients are admitted to the recovery room, but 50% stay less than an hour and a half, 70% have been discharged to their wards by the anæsthetist within two hours, and only 10% remain after three hours, many of the latter being emergency cases admitted in the late evening and retained until morning. Under these conditions prohibiting visitors, save under very exceptional circumstances, seems to cause no hardship to the patients or relatives, and relieves the nursing staff of an unnecessary burden. Visitors are, however, allowed and in fact encouraged in the small neighbouring open-heart recovery room (described in detail elsewhere [3]), where the patient may stay for several days.

To have the head of the bed towards the centre of the room as Dr. Buxton Hopkin describes seems only to add complications; our beds are conventionally placed, and the head of each lies next to a specially designed wall unit with piped facilities mounted in a recessed frame easily removable for servicing. Special recovery-room beds are used, to which the patients are transferred directly from the operating-table, and from which they are moved either to trolleys or to their own beds for return to the wards. These special beds have many advantages which offset their cost. They never leave the theatre floor and are thus less liable to spread infection, they can be easily tilted head up or head down as required, and have side-rails. I do not think the use of ward beds in a recovery room is desirable; and the recovery trolleys found in some centres are inconvenient if the patient is restless or obese.

Finally it is worth emphasising that the best-equipped recovery room is only as good as its nurses; a good sister and experienced staff-nurses are essential if full benefit is to be derived from its use.

Department of Anesthesiology,
The Presbyterian Hospital,
New York 32, N.Y. CYRIL SANGER.

STAPHYLOCOCCI AND DIARRHŒA IN HOSPITALS

SIR,—Your annotation (Feb. 25) has prompted us to report a case which illustrates some of the difficulties in pathogenesis you described. This case also demonstrates that the hazards of the disease are not confined to adult surgical patients, but may be encountered in any environment with virulent staphylococci and susceptible individuals.

A previously healthy 5-year-old boy came into hospital with signs of acute meningitis. This diagnosis was confirmed by examination of the cerebrospinal fluid, from which *Hæmophilus influenzæ* was cultured. No staphylococci were isolated from nose and throat cultures taken on admission. When the purulent cerebrospinal fluid was noted, treatment was begun with penicillin, chloramphenicol, and sulphadimidine.

In spite of some early clinical improvement he remained lethargic. He refused food by mouth, and was nourished by fluids through an indwelling nasogastric tube. He progressively but slowly improved until the 6th day, when he began vomiting and passed green, watery stools without blood or mucus.

The nasogastric tube was removed; and he was maintained on intravenous fluids, and his condition stabilised. But on the 8th day his temperature rose to 105°F and circulatory collapse developed. Blood-pressure was precariously maintained by pressor drugs and hydrocortisone, but he died on the 9th day. The stools cultured the previous day produced a heavy growth of coagulase-positive staphylococci.

At necropsy the meningitis was found to be healed; abnormal findings were limited to the alimentary canal. Intense inflammation and necrosis with pseudomembrane formation were present at the lower end of the œsophagus, stomach, and small intestine. The terminal ileum, colon, and rectum were normal. *Stapylococcus aureus* was cultured from material taken from the nose, throat, and small intestine.

This staphylococcus was of phage-type 83A, identical in type with one isolated from a baby recently discharged from the ward who had had staphylococcal pneumonia. By further search this organism was revealed in the nose of a student nurse working on the ward. By the disc-sensitivity method it was resistant to sulphonamides, penicillin, tetracycline, chloramphenicol, and erythromycin, but sensitive to neomycin, and framycetin sulphate (' Soframycin ').

In retrospect, we realise that because this complication is rare in children with medical conditions, we were neither alert enough to prevent it nor did we institute therapy swiftly enough when it might have proved effective.

The following suggestions on management of ill patients being treated with broad-spectrum antibiotics seem reasonable especially if the œsophagus is intubated via the nose. Serial nasal cultures should be made and the appearance of staphylococci looked on with suspicion; their eradication by means of

1. Bingold, A. C. *Proc. R. Soc. Med.* 1959, **52**, 906.
2. Sadove, M. S., Cross, J. H. The Recovery Room. Philadelphia, 1956.
3. Hanks, E. C., Deterling, R. A., Jr., Himmelstein, A., Scheiner, M., Papper, E. M. *Amer. J. Cardiol.* 1960, **6**, 778.

topical antibiotic applications seems advisable. Stained smears and cultures of the stomach aspirate should be examined frequently, because they may give the earliest warning of enteritis principally involving the upper intestinal tract. Reduction or absence of the normal bacterial flora of the stools may indicate a dangerous degree of susceptibility. Symptoms of lethargy, anorexia, vomiting, or diarrhœa should prompt immediate bacteriological investigation of the stools or vomitus by stalned films; and if organisms resembling staphylococci are found, treatment should be immediate. We now know that a negative stool culture does not rule out staphylococcal enteritis in the early stages and are prepared to start therapy on suspicion. These measures are, of course, complementary to the general precautions routinely taken to prevent the spread of virulent " epidemic " types of staphylococci.

We are grateful to Dr. W. G. Henderson for the clinical pathology reports and his assistance in tracing the epidemiology, to Dr. K. Porter for the necropsy findings, and to Prof. R. E. O. Williams for helpful discussion.

Paddington Green Children's Hospital, London, W.2.

A. B. BERGMAN
T. E. OPPÉ.

ATHEROSCLEROSIS AND CORONARY THROMBOSIS

SIR,—Professor Crawford and his collaborators (Feb. 25) set out with the specific purpose of establishing whether ischæmic heart-disease in men under the age of 40 differs from that in the older age-groups, and cite among other references a letter in which I made this suggestion.[1] They analyse in some detail a series of 75 postmortem records of men who have *died suddenly* from myocardial ischæmia and conclude : "There is nothing to support the contention that under the age of 40 *fatal* coronary disease differs in any essential way from *the disease* in older subjects." (The italics are mine.)

I saw 221 *living* men aged 65-85 years, 80 of whom had angina pectoris and/or electrocardiographic evidence of myocardial ischæmia without infarction. The mean serum-cholesterol, β/α lipoprotein ratio, and pre-β-lipoprotein of this group did not differ from those of the 133 who showed no evidence of coronary disease—whereas the mean serum-cholesterol of 8 other men who had electrocardiographic evidence of an old myocardial infarction was 31 mg. per 100 ml. higher than the controls, a difference which was significant at the 5% level. Several of the 80 have subsequently died of primary causes other than sudden myocardial ischæmia—influenzal pneumonia and cerebrovascular accident to mention two specific instances. For these and other reasons outlined previously [1] I believe that angina pectoris and myocardial ischæmia (without infarction), which makes up the bulk of the coronary heart-disease in my sample, may differ in ætiology from coronary thrombosis (which makes up the bulk of coronary heart-disease in younger men) and may be due to coronary atherosclerosis without occlusion of a major artery. I also concluded with Dr. Graham and Mr. Howard [2] that the factors responsible for thrombosis formation are not the same as those responsible for atherogenesis—although obviously some atherosclerosis is an essential precursor of thrombosis.

Professor Crawford and his colleagues, by restricting their attention to men who have had a lethal occlusion of a major artery—men whose disease is in fact of the same general pattern as that of the 8 from my sample who had suffered myocardial infarction—have not put themselves in a position to comment on the validity of my hypothesis that the bulk of coronary heart-disease among old people is a different entity from acute coronary thrombosis. They have simply shown that the pathological changes underlying sudden death from coronary disease change little between the ages of 26 and 59 years.

In fact, their evidence is in no way incompatible with my conclusions (which together with the data on which they are based are to appear in full soon [3]) and I am greatly encouraged that they, like Professor Morris (Jan. 7), find among their subjects a group who suffered a lethal occlusion with minimal atherosclerosis. Furthermore, I am encouraged that none of these men is over 52 years.

London School of Hygiene and Tropical Medicine, London, W.C.1.

ROY M. ACHESON.

1. Acheson, R. M. *Lancet*, 1960, ii, 706.
2. Graham, C. A., Howard, A. N. *ibid.* p. 527.

CHROMOSOME STUDIES IN LEUKÆMIA

SIR,—Several months ago you were good enough to publish a letter in which we asked for the opportunity of studying the chromosomes of blood and bone-marrow cells of mongols with leukæmia. In consequence of the publication of that letter,[4] and a similar letter in the *British Medical Journal*, we were able within a few months to study 5 such cases as well as the first known instance of the occurrence of mongolism and leukæmia in one sibship. The results of these studies have now been published.[5 6] We are encouraged by the success of our previous appeal to ask again for the opportunity to carry out chromosome studies in certain cases of leukæmia.

We have just prepared for publication an interim report of the results of our chromosome studies in acute leukæmia,[7] other than acute leukæmia in association with mongolism. Of 22 cases of acute leukæmia in adults, 7 gave a history of having had radiotherapy for some disease other than leukæmia within the preceding 12 years. In these 7 cases, we believe there is an increased possibility that leukæmia was radiation-induced.[8] Definite chromosome abnormalities were found in 5 of these 7 cases. In contrast, abnormalities were demonstrable in 3 of 15 cases without a history of previous radiotherapy. Cases of leukæmia with such a history of radiotherapy are probably uncommon, but we feel that their investigation may materially help us in the elucidation of the leukæmogenic risk of radiation exposure. Accordingly we would be grateful for the opportunity of studying such cases before the instigation of treatment for the leukæmic condition. As there is no evidence relating radiation exposure to chronic lymphatic leukæmia, the cases in which we are interested are those of acute leukæmia and chronic myeloid leukæmia with a significant exposure history. For this purpose significant exposure history means having received a therapeutic dose of a radioisotope or treatment with either X rays or radium to any part of the trunk, other than for skin diseases, at any time during the 12 years prior to the diagnosis of leukæmia.

The blood and bone-marrow samples we require are taken in the usual way, and this can be done at the same time as samples are taken for diagnostic purposes. Although materials for chromosome studies require special handling immediately after they are taken, we would be glad of the opportunity of studying, anywhere in Britain, cases of leukæmia which may be radiation-induced.

Clinical Effects of Radiation Research Unit, Medical Research Council, Western General Hospital, Edinburgh.

A. G. BAIKIE
W. M. COURT BROWN
PATRICIA A. JACOBS.

SIR,—Miss Tough and her coworkers (Feb. 25) state: " An abnormality of polymorphonuclear lobulation has been described in mongols (Mittwoch 1958)." But Mittwoch [9] herself in an earlier paper wrote: " Turpin and Bernyer [10] showed that the Arneth index of 42 mongols was different from that of their normal relatives and from

3. *Brit. J. prev. soc. Med.* 1961 (in the press).
4. Baikie, A. G., Court Brown, W. M., Jacobs, P. A. *Lancet*, 1960, i, 1251.
5. Buckton, K. E., Harnden, D. G., Baikie, A. G., Woods, G. E. *ibid.* 1961, i, 171.
6. Tough, I. M., Court Brown W. M., Baikie, A. G., Buckton, K. E., Harnden, D. G., Jacobs, P. A , King, M. J., McBride, J. A. *ibid.* p. 411.
7. Baikie, A. G., Jacobs, P. A., McBride, J. A., Tough, I. M. In preparation.
8. The Hazards to Man of Nuclear and Allied Radiation. Report to the Medical Research Council. H.M. Stationery Office, London, 1960.
9. Mittwoch, U. *J. ment. defic. Res.* 1957, **1**, 26.
10. Turpin, R., Bernyer, G. *Rev. Hemat.* 1947, **2**, 189.

the general population." I think that in such a fashionable subject as mongolism, this historical point is worth mentioning.

Clinique de Génétique Médicale,
Hôpital des Enfants-malades,
Paris, 15e, France. JEAN DE GROUCHY.

BARR BODIES

SIR,—The letter of Dr. Fraccaro and Dr. Lindsten [1] on the difficulties of any simple interpretation of the relationship of the Barr bodies to the X chromosomes leads me to offer some preliminary observations on another case.

An intelligent married woman of good physique presented with primary amenorrhœa. Examination of the buccal mucosa (Dr. A. I. Spriggs) revealed unusually numerous, large, and prominent Barr bodies, many with a bilobed structure; about 5% of nuclei with a Barr body contained 2 discrete Barr bodies, which were always close together. In the vaginal smear were very large Barr bodies but no double representation. Drumsticks (13/1100) were observed in the neutrophils—a rather low proportion. Most appeared somewhat larger than normal (an observation for which I am indebted to Dr. Spriggs) and about half were sessile.

On cytological examination of a colchicine-treated fibroblast culture a consistent aberration in over 20 consecutive cells was observed. Visual analysis revealed a normal karyotype apart from the absence of one chromosome and the presence of an abnormal chromosome. (In some cells the satellites were unusually easy to see, and clearly present on at least 5 of the large acrocentrics and at least 3 of the small acrocentrics; but further experience has confirmed that these are not abnormal findings.) Unusual difficulty was experienced in identifying chromosomes X, 7, 9, and 11. (The X is regarded as shorter and more metacentric than the 6th autosome.) Only 7 chromosomes could be defined in this group: the abnormal chromosome appeared to resemble most closely a 9th chromosome with the addition, attached to the long arm, of a length of chromosome approximately equal to the long arm of an X. In view of the associated features of normal physique, good intelligence, primary amenorrhœa, and large Barr bodies, the most likely interpretation appears to be translocation of an extra long arm of an X chromosome on to the long arm of an autosome of similar proportions, or possibly on to the long arm of another X. That is, there are 3 long arms and 2 short arms of X chromosome, although the chromosome to which the third long arm is attached has not yet been identified with confidence.

It seems clear from this case that:

(1) Abnormalities of the Barr bodies are quite compatible with good intellect, although the fact that many surveys have been conducted in hospitals for mental defectives may have exaggerated the dissociation in published cases.

(2) The Barr bodies cannot have any simple numerical relationship to the short arms of the X chromosomes.

(3) The Barr bodies cannot have any simple numerical relationship to the long arms of the X chromosomes, as, when the Barr bodies appeared to be duplicated, they were always close together, unlike the usual findings in the triple-X syndrome.[2]

(4) The Barr bodies cannot have any simple relationship to the number of intact X chromosomes. It may be added that a very careful examination of the bilobed and double Barr bodies showed no suggestion of inequality of the two parts.

(5) The redundancy hypothesis, which postulates that the 2nd and other X chromosomes, and possibly extra autosomes, are slung on to the nuclear membrane in an inert state, is not compatible with the observations above. Nor is it easily compatible with the apparent inequality in volume between the Barr body and even the short arm of the X chromosome.

1. Fraccaro, M., Lindsten, J. *Lancet*, 1960, i, 1303.
2. Lennox, B. Personal communication.

I may add that a search for abnormal bodies, about half the size of a Barr body, in the 3 cases of trisomy 17, all female, that I have seen, was unrewarding. The neutrophils from two cases were examined; these showed a normal lobe distribution and drumstick proportion, but there was no consistent structure half the size of a drumstick. I am grateful to Dr. F. G. Bolton for confirming the normality of these cells.

It is possible to offer as a consistent explanation the suggestions that the part of the X chromosome related to the Barr body occupies part of the long arm, and that the abnormal chromosome consists of a normal X chromosome, to the long arm of which an additional long arm of an X chromosome is attached. The two parts related to the Barr body would then be connected by a length of chromosome not participating in Barr-body formation, thus allowing duplicity, but never distant separation, of the Barr bodies. This argument is weakened by a circular strand in that the primary, if uncertain, observational judgment on the chromosomal aberration has been " corrected " in order to conform to a simple hypothesis relating the Barr body exclusively to the X chromosome. If such hypotheses are used as an alternative, or even as an aid, to the identification of the X chromosome, cytological studies are in danger of spuriously confirming these hypotheses and of imposing an erroneous uniformity on the chromosomal analyses of cases picked up on buccal-smear surveys.

Children's Hospital of Philadelphia,
Pennsylvania. J. H. EDWARDS.

CHROMOSOME TRANSLOCATIONS IN MAN

SIR,—Your editorial [1] on the mongol chromosome and others drew attention to translocations. The practical and theoretical interest of these justifies comment.

The first recorded example was the 22/13 translocation,[3] but 6 others are now known. Some involve the mongol chromosome: 21/13 or /14, or /15,[3] 21/22,[4] or 22/22, 21/21,[5] 21/15.[4 6] You stated [1] that these explain the occurrence of " exceptional 46-chromosome mongols ", and of the rare cases where 2 sibs are affected.[4 6] Other translocations have been reported: 14/15,[7] 22/13,[8] and a possible 21/Y.[9]

Thus translocations appear to play a well-defined role in pathology. It is noteworthy that all the types so far recorded involve acrocentric chromosomes. This kind of rearrangement is, of course, most easily recognised, for reciprocal interchanges between metacentric elements of comparable size would be difficult to assess, and would merely lead to wrong classification when establishing the karyotype. Thus, the observations may be biased. But the presence of satellites in nos. 13, 14, and 21 could play a role in the translocation mechanism, and in determining the probability of its occurrence.

Furthermore, the so-called " centric fusion " implies a deletion of the chromosomal segments attached to the eliminated centromere. Hence the more acrocentric the elements, the smaller will be the chromosomal loss. In view of the possible lethal effect of big autosomal deletions (none has been observed as yet) this prevalence of translocations between acrocentric chromosomes could well result from natural selection.

The practical interest of translocations is not restricted to genetic counselling in familial mongolism. The 14/15 type

1. *Lancet*, 1960, ii, 1068.
2. Turpin, R., Lejeune, J., Lafourcade, J., Gautier, M. *C.R. Acad. Sci., Paris*, 1959, **248**, 3636.
3. Polani, P. E., Briggs, J. H., Ford, C. E., Clarke, C. M., Berg, J. M. *Lancet*, 1960, i, 721.
4. Penrose, L. S., Ellis, J. R., Delhanty, J. D. A. *ibid.* 1960, ii, 409.
5. Fraccaro, M., Kaijser, K., Lindsten, J. *ibid.* 1960, i, 724.
6. Carter, C. O., Hamerton, J. L., Polani, P. E., Gunalp, A., Weller, S. D. V. *ibid.* 1960, ii, 678.
7. Lejeune, J., Turpin, R., Decourt, J. *C.R. Acad. Sci., Paris*, 1960, **250**, 2468.
8. Moorhead, P. S., Mellman, W. J., Wenar, C. *Amer. J. Genet.* (in the press).
9. Turpin, R., Lejeune, J., Gautier, M. Conference on Congenital Malformations, London, July 18–22, 1960.

was found in an individual also exhibiting the XXY Klinefelter syndrome.[7] A mother carrying a balanced 22/13 translocation gave birth to a classical mongol with 47 normal chromosomes and 3 no. 21 chromosomes, and without the maternal translocation.[8] The fact that translocations seem to increase the probability of non-disjunction in *other* chromosomes invests the discovery of a translocation in an apparently healthy individual with eugenic significance. The diagnostic interest of translocations is mainly dependent on their phenotypic consequences. For example, all the healthy carriers of the different 21/13 varieties with a balanced 45-chromosome genotype have been reported to be normal. The " exceptional 46-chromosome mongols " are phenotypically indistinguishable from classical trisomics.

A possible conclusion would be that the loss of satellites does not have harmful effects, because of the low genic content of these segments.

By contrast the two varieties of the 22/13 type seem harmful. In the first case (multiple vertebral dysgenesis) [7] vertebral deformities and mental and physical retardation were observed. The second example,[8] observed in a mother and in 4 of her children, determined various degrees of speech defect and mental retardation, ranging from very severe in the children to normality in the mother.

These intrafamilial variations between carriers of the *same* variety demonstrate the influence of the rest of the genotype. But the interfamilial variation between different varieties of the same type could be attributed to the extent of change in each variety—i.e., the eliminated fragments could differ.

If the effect of position is ignored, at any rate in a preliminary survey, a sample of, say, 20 varieties of the 22/13 type could yield much information about the genic content of the eliminated fragment. For example, if it was observed that 2 characters, which are sometimes independent, are always accompanied by a 3rd, when both are present together, a three-point linkage map would be obtained; and its spatial relationship to the centromeres could be established. To determine whether the eliminated fragment belonged to no. 22 or to no. 13 would depend upon comparisons between types 22/13 and 22/15.

The method is limited by the shortness of the analysable fragment. This is due to the harmful effect of autosomal deletions.

Some types in which the deleted fragments are genetically quite inactive could very well be transmitted unknowingly in our species. Thus, a possible polymorphism of the karyotype among apparently normal people, even though very rare,[7] cannot be ruled out.

This discussion of cytogenetic mapping of chromosome segments would probably have been considered unrealistic a year ago. But with the worldwide expansion of research in cytogenetics, the requisite sample of many varieties of the same type is likely to be obtainable fairly soon.

It would be beneficial if authors working in this field gave as much attention to precise phenotypic description as to accurate chromosome analysis.

Institut de Progenèse,
Hôpital Trousseau,
Paris, 12e.

RAYMOND TURPIN
JÉRÔME LEJEUNE.

METRIC SYSTEM IN PRACTICE

SIR,—The possible error Dr. Dawkins (March 4) mentions, due to shifting the decimal point in the wrong direction when using the metric system, is avoided by following the advice given in many foreign pharmacology books—i.e., writing out *in full* the dose in milligrammes.

Thus not ·010 g., but ten milligrammes is written in full on the prescription, and also the words, half, a quarter, &c., are spelt out. This also has the advantage of concentrating the attention of the prescriber on the dosage. When we deal with centigrammes the usual numeral writing can be used, but it is safer instead of relying on the simple point—usually invisible—to write a zero with a comma after it thus: 0,50 (not ·50).

Accidents cannot occur with the metric system when care is taken; but the apothecaries' system leads to many accidents, either through bad design of the symbols or, more frequently, when preparing solutions of powerful drugs and endeavouring to change grains per pint into milligrammes per litre. The metric system is safer.

London, W.1. A. P. CAWADIAS.

POSITIONING FOR GALLBLADDER SURGERY

SIR,—The letter from Mr. Fauset Welsh (Feb. 11) prompts me to suggest an alternative method which has been appreciated by the surgeons with whom I have worked during the past ten years.

The method is to place 2 large firm pillows lengthways over the upper two-fifths of the operating-table, one on top of the other, with the lower a few inches further towards the feet, thus forming a " step " which supports the lumbar curve. The unconscious patient on his canvas is then placed supine on the table so that the lower edge of the top pillow lies directly beneath a point about two inches below the xiphisternum. A 3rd pillow is placed under his knees.

The table should be tilted foot down about 10° and given a 5° left lateral tilt: this encourages the liver and other abdominal organs to fall away from the thorax towards the left pelvic cavity. The upper pillows open the thoracic outlet without producing the backbreaking effect of the old-fashioned " bridge "; the pillow under the knees is an asset to any intra-abdominal procedure—it produces upward rotation of the pelvis, which besides increasing abdominal relaxation permits the spinal column to rest fully supported, so minimising the postoperative " backache " one associates with overstretched spinal ligaments " carrying the can " for curarised spinal supporting muscles. The weight of the patient's legs is also supported over a wider area, making thrombosis of the calf vein less likely.

Royal East Sussex Hospital,
Hastings. W. R. MURPHY.

RADIOACTIVE DRINKING-WATER AND CANCER

SIR,—There has been little comment on the suggested link between " unexpected variations in cancer incidence apparently related to water-supplies " [1] and high radioactivity in West Devon drinking-water.[2]

Although an " intensive integrated programme of measurements both of radioactivity and trace elements . . . with a social survey " is being carried out in West Devon, is there not an urgent necessity to support this work by similar surveys elsewhere—for the following reasons?

(1) The Devon work suggests that natural radioactivity in drinking-water, which has been regarded as very small and " negligible " (2% of " natural background "),[3] may be a significant cause of cancer of all types.

(2) Some cancer may possibly be prevented by substituting drinking-water of low radioactivity.

(3) " As a precautionary measure all the appreciably radioactive water-supplies in West Devon have been cut off and replaced by inactive supplies." [2] Is this not necessary elsewhere?

(4) Four of the nine examinations of West Devon reservoir water samples showed high radioactivity. Is water no longer being drunk from these reservoirs?

(5) Devonian geological strata (" old red sandstone "), from which the highly radioactive water comes in West Devon, is widely found in South Devon, Cornwall, Somerset (Exmoor and the Quantocks), a large area of South Wales, the southern

1. Allen-Price, E. D. *Lancet*, 1960, i, 1235.
2. Abbatt, J. D., Lakey, J. R., Mathias, D. J. *ibid.* 1960, ii, 1272.
3. Hazards to Man of Nuclear and Allied Radiations. Report to the Medical Research Council. H.M. Stationery Office, 1956.

highlands of Scotland, and along the east coast of Scotland to the Orkneys.

(6) Highly radioactive waters are known to occur away from surface Devonian strata—e.g., at spas. But the M.R.C. 1960 report states that only 60 specimens of potable water have been examined in Great Britain, in addition to the 51 examinations reported in *The Lancet*.

(7) New reservoirs are being made or suggested in many parts of the country (e.g., Birmingham and Devon), and some new water-supplies are being made from " bore holes " several hundred feet deep (Exmouth). Is it not common sense to examine the radioactivity of these new water-supplies *before* money is spent in making new reservoirs?

Cricket Malherbie,
Ilminster,
Somerset.

GEOFFREY TAYLOR.

ORIGINS OF CRIME

SIR,—In your annotation (Jan. 7) commenting on the McCords' findings,[1] the statement that " methods of discipline used—punitive or love-orientated—was not important " is misleading.

Though they state (p. 78) " consistency of parental behaviour is more important than the methods parents use ", on p. 132 they point out that love-oriented methods militated against crimes of violence, and (p. 169) that boys disciplined in an erratically punitive manner were most likely to commit every type of crime, except traffic violations, and were less likely to reform in later life. In their summing-up (p. 184) they comment: " Consistently love-oriented discipline can overcome many of the harmful effects of otherwise unhealthy homes. Since inconsistent punitiveness has been shown to be definitely harmful, we would suggest that a valuable method of crime prevention is the education of parents in the use of non-punitive, yet consistent, methods of discipline. " These findings are consistent with those of Glueck and Glueck [2]—that the use of physical punishment had a positive relationship to crime, and that the parents of non-delinquents depended more on reasoning with the child. This carefully collected evidence is precisely the reverse of popular mythology and the views of the judiciary on the topic of parental discipline, and surely deserves the widest publicity.

University of Otago Medical School,
Dunedin, New Zealand.

JOHN R. E. DOBSON.

EXTERNAL CARDIAC MASSAGE

SIR,—The recent correspondence on external thoracic compression as a method of cardiac massage prompts me to record my own experience, as I now have a series of two.

The first occasion, about four years ago, was a few minutes after giving an injection before an intravenous pyelogram. The patient, a fairly fit man of 57, collapsed completely, there was no respiratory effort and no radial pulse. I tore open his night-shirt and could hear no heartbeat. I was rather annoyed (and probably frightened), cursed him loudly, and supplemented the cursing with a blow on the præcordium. He gasped, respiration and heart-sounds reappeared, and within 5 minutes he was conscious and back to normal. There were no sequelæ.

The second was today, and I had just related the story to my wife when she read your correspondence—hence this letter.

A man of 65 had taken a number of unknown tablets and was admitted deeply comatosed. I had a quick look at him, noting pinpoint pupils and a strong, albeit slow, heartbeat. I went out to get a sphygmomanometer and when I returned the sister said he was dead. There was no pulse, heartbeat, or respiratory movement and his pupils were a lot larger than before. I agreed and said we would leave it to the pathologist to find out what was in his stomach, and gave the patient a parting thump on the chest. He gasped, heartbeats returned. His airway was cleared and nikethamide given intravenously. In less than 5 minutes he was a good colour, breathing regularly at a normal rate, his blood-pressure 130/70 mm. Hg and the pupils were again pinpoint. He has recovered completely.

In both cases my action was quite fortuitous, but it seems that a solid punch on the chest can occasionally do more than merely give vent to the exasperation of the doctor who feels that he has failed.

Norfolk and Norwich Hospital,
Norwich.

TERENCE MCGOVERN.

1. McCord, W., McCord, J. Origins of Crime. London, 1960.
2. Glueck, S., Glueck, E. Unravelling Juvenile Delinquency, New York, 1950.

TOXIC REACTIONS TO IRON DEXTRAN

SIR,—The article by Dr. Ben-Ishay (March 4) condemns a very useful drug (iron dextran), but on the evidence of only 11 cases. The drastic action he proposes seems unjustified. Many other causes of pyrexia seem to have been excluded on inadequate grounds.

C. M. GRUNDLINGH.
N. F. SAHHAR.

London, W.3.

SIDE-EFFECTS OF TRANYLCYPROMINE

SIR,—Tranylcypromine (' Parnate '), an antidepressant drug of monoamine-oxidase-inhibitor type, has recently become generally available in this country.

In the past few months I have carried out a clinical trial of its efficacy in treating depressive states. During this time the drug was given to 30 patients, 14 with reactive depressions, and 16 with endogenous depressive states. Because of the small numbers I came to no firm conclusion about its therapeutic effectiveness; but I noted that any improvement usually took place within forty-eight to seventy-two hours, thus substantiating the maker's claim of rapid action.

Side-effects were observed in 3 patients; and I regarded these as sufficiently serious to discontinue the trial meantime. They took the form of sudden and severe occipital headache, spreading to the vertex, with associated pallor. The blood-pressure was raised and the pulse was slow. Photophobia was noted in 2 patients, and vomiting in 1. All 3 had neck-stiffness. No other abnormalities were detected in any system. This acute phase lasted for approximately one hour; and the clinical condition of the patient during this time was poor. Over a period of four to six hours the headache became less severe and within twenty-four to forty-eight hours the symptoms had completely disappeared.

CASE 1.—A woman of 34, diagnosed as reactive depression with schizoid features, with no physical abnormality on admission. After three weeks on tranylcypromine (10 mg. t.d.s.) she suddenly developed severe occipital headache spreading to the vertex. She was pale and collapsed, with slight neck-stiffness, and photophobia, and she disliked examination. Her blood-pressure was 175/120 (previously 115/70) and pulse-rate 48. The acute phase lasted an hour; headache was less severe over four to six hours; and she recovered completely in forty-eight hours.

CASE 2.—A woman, aged 38, with reactive depression and no physical abnormality, had occipital headache with spread to the vertex, and vomiting, after one week on tranylcypromine, 10 mg. b.d. She was cold and sweating; her blood-pressure was 170/120 (previously 122/76), and pulse-rate 60. Subsequent course as in case 1.

CASE 3.—A woman of 34, with reactive depression and no physical abnormality, suddenly had severe headache after taking tranylcypromine, 30 mg. daily, for five days. She had neck-stiffness and considerable photophobia. Her blood-pressure was 165/105 (formerly 125/75), and pulse-rate 54. The severity of the headache lessened over six to eight hours, the course otherwise being as in case 1.

These 3 patients had no history of hypertension, headache, or any previous drug-reaction, and no evidence of physical disorder. No other drugs apart from tranylcypromine were being taken at the time. The headache was severe and blinding, and in 2 of the patients the diagnosis of subarachnoid hæmorrhage was considered in the initial stages. In all 3 the

condition resolved with bed rest after stopping the drug. No residual effects were noted.

In view of the sudden onset and hypertensive nature of these side-effects I would suggest that, until their significance can be determined, this drug should be administered with considerable caution, particularly in outpatients.

Crichton Royal Hospital,
Dumfries. JOHN A. CLARK.

SURGERY OF THE PAINFUL HIP

SIR,—I have only just seen Mr. Thethravusamy's reply (Jan. 28) to my letter of Dec. 17.

I found pain in the hip to recur in a few cases; this was because I had cut only the superficial tendon and not the fibres in the muscle. I now cut through the muscle, and have had no more recurrences.

Two days after the tendon and muscle have been divided the patient should walk, increasing the distance gradually to 2 or 3 miles daily.

I think pain is caused by a streptococcal infection of the gracilis tendon. I put an inch of tendon in sterilised milk (200 ml.) containing 1:400 carbolic acid. After 2 weeks diplococci (streptococci) developed. After seeing many cases, I believe that painful hip begins with a shortening of the gracilis tendon, which eventually leads to displacement of the hip, and to rheumatism.

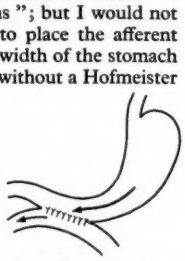
The best results are obtained where the hip, or hips, alone are involved. But when the femur is out of the acetabulum walking remains difficult, though the hip is no longer painful.

London. W.1. V. NESFIELD.

GASTRECTOMY AND THE BLIND-LOOP SYNDROME

SIR,—The article by Mr. Kinsella and Dr. Hennessy [1] is so excellent and helpful that I hesitate to cross swords with them.

I am entirely in agreement with them on the need for "quiet confluence of unobstructed streams"; but I would not agree that to obtain this it is necessary to place the afferent loop to the lesser curvature. If the whole width of the stomach is being used for the anastomosis, with or without a Hofmeister valve, then I think they are correct; but if the anastomosis is made according to the method I described [2] in which the right-hand portion of the divided stomach is used to make a new lesser curve and the greater-curve end of the divided stomach only is used for the anastomosis, undoubtedly a better confluence of streams is obtained by placing the afferent loop to the greater curve.



On follow-up of 85 patients who have had this type of operation I was much impressed by the easy passage of barium into the efferent loop with no radiological evidence of undue filling or stasis of the afferent loop. For the past twelve months I have been doing elective vagotomy and gastroenterostomy as an alternative to gastrectomy for duodenal ulcers, and the very satisfactory emptying obtained with the above type of anastomosis has led me to do a similar anastomosis after vagotomy. The greater omentum is freed from the distal 3 in. or more of the stomach and the greater curve near the pylorus is used for anastomosis to a loop of jejunum running from left to right, making the afferent loop as short as possible.

The loop is placed in front or behind the colon according to the length of mesocolon and disposal of the mid-colic vessels. I have found on doing barium meals that the stomach emptying is definitely better than when a posterior vertical gastroenterostomy has been done. With this procedure we have had virtually no stasis in the stomach after vagotomy. I do not think it is right to say that vagotomy inevitably adds retention, and indeed our evidence shows that it has little effect in increasing the "reservoir action" of the stomach.

Mary Calvert Holdsworth
Memorial Hospital,
Mysore City,
South India. FRANK I. TOVEY.

1. Kinsella, V. J., Hennessy, W. B. *Lancet*, 1960, ii, 1205.
2. Tovey, F. I. *ibid.* p. 1209.

SEX AND PSYCHIATRY

SIR,—It can only benefit both, if psychiatry and general medicine become better integrated. Influences beyond its control, and technical isolation, have sometimes forced psychiatry into unscientific methods, and the light of modern knowledge must shine into the dark corners.

A typical example—almost incredible to other branches of medicine and surgery—is that in many mental hospitals consultant psychiatrists are still labelled, and have to work in rigid categories, treating male or female patients only.

This is clearly an antiquated, unscientific administrative convenience, typical of many from which psychiatry has suffered. Is it too much to hope that this anachronism will rapidly be abolished?

Ealing,
London, W.13. R. E. W. OLIVER.

BEHAVIOUR THERAPY IN TRANSVESTISM

SIR,—Your stimulating leading article (Pavlov or Freud) and the interesting and successful result of the application of behaviour therapy to the treatment of transvestism, reported by Dr. Barker and his colleagues (March 4), prompts us to report a similar case we successfully treated here in 1960 by a similar method.

A man of 27 had been in the habit of dressing in female clothes since the age of 14. While his wife was away at work he dressed as usual in her clothes and went out shopping. He was apprehended by the police and referred for psychiatric examination. Over 4 years the marriage had never been consummated owing to his wife's frigidity.

He was admitted to hospital and treated along the lines outlined by Raymond.[1] Apomorphine hydrochloride (gr. $^1/_{20}$–$^1/_8$) was injected intramuscularly 2-hourly for 4 days and nights. After injection he was asked to dress entirely in women's clothing, and he wore this throughout the period of nausea and vomiting. Apart from losing 1 lb. in weight he remained in good physical condition.

After 4 days' treatment the patient exhibited marked revulsion at the sight of female clothes and flatly refused to put them on. He no longer felt any desire to wear them, and this was still so when he was examined 7 months later.

His wife's frigidity, which was coincidental and unconnected with his transvestism, was treated in outpatients by reciprocal inhibition as described by Wolpe [2]; the success achieved can be gauged by the fact that she is now pregnant, and the marriage is happily stabilised.

Aversion therapy may seem time-consuming and temporarily unpleasant for the patient, but it appears to be effective.

Our purpose has not been to explain how aversion therapy works, but to confirm that with it transvestism can be successfully treated. The condition is adequately described in most psychiatric textbooks, but its treatment is not.

Whittingham Hospital,
near Preston,
Lancashire J. D. GLYNN
P. HARPER.

SIR,—I was interested to read about the case of transvestism treated by aversion therapy by Dr. Barker and his colleagues.

Apomorphine, used on its own, can be equally effective

1. Raymond, M. J. *Brit. med. J.* 1956, ii, 854.
2. Wolpe, J. Psychotherapy by Reciprocal Inhibition. 1958.

without aversion. Dr. J. Y. Dent, who developed the modern treatment of alcoholism with apomorphine,[1] claims that it acts on the basal centres of the brain and that its action is of a chemical nature.

Dent also treated psychotic and neurotic patients with apomorphine[2 3] and had many successes. In all his cases apomorphine was used alone with no recourse to aversion.

May I hope that Dr. Barker and his coworkers use this technique when confronted by their next psychiatric problem? It is less cumbersome and equally satisfactory.

Romford, Essex. LEON M. SHIRLAW.

PAVLOV OR FREUD

SIR,—Professor Eysenck's attempt to evaluate the role of conditioned reflexes in the neuroses is surely to be welcomed. But to interpret the neuroses as a series of bad habits acquired as conditioned reflexes is not entirely consistent either with the clinical features or with the physiological facts.

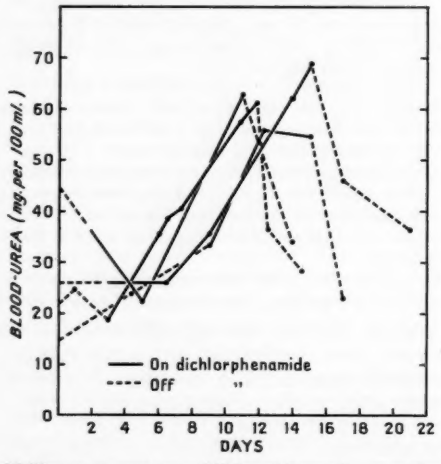
It has long been established that the natural balance of conditioned reflexes can be disturbed as a consequence of fatigue or hormonal changes—two important ætiological factors in neurosis. The conditioned response may become excessive or insufficient, or it may even be reversed. Thus salivation may be inhibited at the sight of food: this does not signify any ulterior motive but a physical derangement of the reflex arc.

To interpret neurotic responses solely in terms of the normal, purposive, conditioned-reflex mechanism, therefore, seems hardly satisfactory. Surely it is time for us to evaluate the significance of these pathological changes in conditioned reflexes—phasic changes as Pavlov called them—in the neuroses, the psychoses, hypertension, dyspepsia, and all those functional disturbances in which the question is pertinent.

Sheffield. C. H. FOGGITT.

DICHLORPHENAMIDE FOR RESPIRATORY INSUFFICIENCY

SIR,—Dr. Simpson (Jan. 7) comments on some toxic effects of dichlorphenamide. We have treated 7 patients with 50 mg. of dichlorphenamide four times daily, and



would like to report an additional hazard—namely, a rise in blood-urea, observed in 4 of our 7 patients. The graph shows the time-relationship of this rise, the height attained, and the rapid return to normal after therapy was stopped.

In the patients with raised blood-urea, urinalysis was normal throughout the period of observation. 1 patient had a typical attack of right renal colic when his blood-urea was 60 mg. per 100 ml. An intravenous pyelogram one week later revealed no abnormality. Renal colic was reported by Yates-Bell[1] in a patient on acetazolamide, which is allied in structure and mode of action to dichlorphenamide.

No cause for the rise in blood-urea has been established, but we hope to carry out renal-clearance studies with this in mind.

Anorexia and nausea were noted by 5 of the patients, including 3 of the 4 whose blood-urea rose. 2 patients, 1 of whom had an elevated blood-urea, complained of mild headache. There is nothing to suggest that this relatively slight rise in blood-urea is related to these symptoms.

Brompton Hospital, S.W.3. E. WAHL
C. F. MCCARTHY.

STERILISATION

SIR,—If the ideal method when planning central sterile supply departments (C.S.S.D.S) is to integrate them into the pharmaceutical department, as suggested by Mr. Wing (March 4), then I wonder why this system has not been adopted in the U.S.A., Canada, and European countries. The majority of C.S.S.D.S in these countries are departments in their own right, with a consultant bacteriologist controlling the methods used and a trained nurse superintendent in day-to-day charge.

No-one is suggesting that the pharmacist is not trained or not able to undertake sterilising, but it is not the pharmacist who will decide upon the contents, containers, sterilising process, and labelling, but the medical and nursing staff whose sole responsibility these are.

It is surely beside the point to suggest that assembling and distributing packs present no greater difficulty than the manufacture of intravenous fluids and injections, etc., since the two are not comparable. The latter is a pharmacist's work, the former a nurse's. A department can be run on factory lines up to a point, but the fact remains that medical work is constantly changing and so are the staff, and there are times when individual needs must be met, as with theatre packs.

This is where the work of the C.S.S.D. becomes very much the concern of the nursing and medical staff, because the procedures undertaken in the wards are initially laid down and carried out by them. A trained nurse, with her knowledge of the scores of nursing procedures (sterile and non-sterile) is the obvious person to supervise and run such a department, particularly as it is a full-time occupation.

It is not merely a question of assembling simple or complex packs, but of being fully conversant with the exact use of the contents in the wards, departments, and theatres—procedures that are quite outside the scope and knowledge of the pharmacist. The impersonal approach is all very well when dealing with the manufacture of drugs, but when dealing with ward-sisters and medical staff it is essential that the person in charge knows something of their problems and difficulties.

C.S.S.D.S in hospitals in this country with trained nurse superintendents in charge are running smoothly. Do the medical staff and matrons consider that these departments could be run more efficiently and economically by pharmacists. Perhaps they may care to comment?

Central Syringe Department, St. Thomas's Hospital, London, S.E.1. F. TOOLE STOTT.

SIR,—Mr. Harris and his colleagues (March 11) should have read my letter (Feb. 18) more carefully before replying to it. I agree with their views.

Public Health Laboratory Service, Middlesbrough, Yorkshire. ROBERT BLOWERS.

1. Dent, J. Y. Anxiety and its Treatment. London, 1955.
2. Dent, J. Y. *Brit. J. Inebr.* 1934, **32**, 65.
3. Dent, J. Y. *Med. Pr.* 1961, **245**, 135.

1. Yates-Bell, J. G. *Brit. med. J.* 1958, ii, 1392.

SIR,—We have followed the correspondence on sterilisation with great interest, in particular the letter of Mr. Harris and his colleagues (March 11).

We consider the logical solution is to employ the department most satisfactorily equipped for the task.

Anyone can operate sterilising equipment after very little instruction, the method adopted varying with the material to be sterilised.

Of paramount importance is sterilisation itself, which can only be effectively achieved by proving that certain bacteria have been destroyed—usually the concern of the pathologist. His domain is not only equipped for proving the point, but is also staffed by those whose training and qualifications are concerned mainly with this subject, and not, as in the case of pharmacists, only a small part of it.

Pathology Department,
Rainhill Hospital,
near Liverpool.

WM. STIRRUP
B. P. HARDMAN.

REPRINTS

SIR,—While your correspondents have been expressing personal approval and distaste of various methods of giving and requesting reprints, those of the *New Scientist* (Feb. 9 onwards) have been discussing proposals for publishing research papers as separates, not in parts of journals. Such proposals are not new; practical schemes have been put forward but it has proved extraordinarily difficult to get them accepted.

Most of us agree that research results should be made available to as wide a public as possible and yet we prefer to send our reprints to " reputable " persons and institutions which are more likely than unknown ones to have easy access to the journals. Is it possible that some of the difficulties in adopting more practical methods of publication are to be found in the mixture of exhibitionism and secretiveness, generosity and acquisitiveness, pride and timidity that motivate the exchange of reprints at the personal level, and that a short-cut to the acceptance of more rational methods of dissemination might be found by recognising these?

Pædiatric Research Unit,
Guy's Hospital Medical School,
London, S.E.1.

M. L. J. ABERCROMBIE.

SIR,—Though none of your correspondents has so far actually said so, I suspect that part of the antagonism to printed reprint request cards arises from a feeling that the wholesale practice of asking authors for reprints constitutes blatant scrounging, and is part of the allegedly modern decadent " something for nothing " attitude to life, sheltering perhaps behind the grand ethic of scientific cooperation. It is felt that to beg a copy of his publication from the author, rather than to purchase it from the publishers as one does a straightforward book, is an act justified only by special circumstances which require a personal letter to explain them.

In " the old days " the presenting of copies of his works was a compliment spontaneously paid to known colleagues by an author at his own expense. In these modern times, when institutions are glad to shoulder the expense of distributing their employees' reprints for the sake of the publicity, the idea has grown up, especially among young newcomers to research, that the distribution of free copies of his work to all who desire them is a normal part of an author's role and duty in community life. Novelists of equable temperament would perhaps find this idea rather amusing.

Admittedly the dissemination of scientific information is not novel writing, but many would maintain that the difference is only one of degree, and moreover a difference which used to be rather smaller than it is today. Admittedly also, publishers of scientific journals do not usually make separates of individual papers commercially available. Perhaps this is one more point to be borne in mind when considering the question of possible reorganisation of the whole machinery of the publication, collocation, and distribution of scientific literature.

The attitudes that I have sketched perhaps belong to an old-fashioned world of individual independent scientific activity, and are inappropriate to the present-day world of large-scale grant-financed institutional research. But they are not yet entirely dead, and it is no bad thing to be reminded of them.

London, W.C.1. K. A. REYNOLDS.

SIR,—So far in this correspondence no-one has mentioned the economic factor—an important consideration. The author of an interesting paper is presumably willing to bear a modest cost for the distribution of a limited number of reprints, but why should he bear a large cost if the demand for reprints is inordinately great?

If it became the accepted practice to enclose a remittance, covering the cost of reprint and postage, when requesting a reprint from someone not a personal acquaintance, the position would be different. If the demand for reprints exceeded the available supply, surplus requests and remittances could be sent to some central agency, who would distribute photostat copies. Alternatively the journal itself might run its own reprint service to deal with requests, other than from the author's personal friends.

When studying a particular subject, a file which can be referred to at a moment's notice, built up of reprints of relevant articles, is most valuable. Surely it cannot be considered improper to pay for reprints when we can so readily buy textbooks and journals.

Bedford General Hospital,
Bedford. R. G. MILLER.

SIR,—The number of reprints I order depends on the estimated requirements, and on the state of the departmental funds (usually 200 or £5-worth, whichever is the greater). Then requests are arranged in this order of priority:

(1) Friends, and coworkers in the field.
(2) Letters.
(3) Signed printed cards (with preference given to those from remote parts of the world, or in Latin).
(4) Unsigned printed cards.
(5) Cards asking for several copies.

One American organisation has an excellent scheme of using an envelope for the request which, by reversing the flap, becomes reply-paid for returning the reprint.

c/o The University of Chicago,
Chicago, Illinois. D. N. BARON.

SIR,—When we consider that the torrent of medical literature is rising into a flood, it is evident that the distribution of reprints between those interested in a particular subject is becoming an increasingly important way of maintaining contact with new research. I have always made a point of asking for reprints by a letter in which I discuss the work published and comment on it. This not only serves to reduce my enthusiasm for asking for reprints which are scarcely worth having, but it has also given me the opportunity of making friends and learning much about work related to my own interests, which I would not have done otherwise.

This system breaks down, however, when one's acquaintance with a particular paper is derived from an abstract in a journal and the paper itself is written in a language one cannot read. If the work seems important there is scarcely any alternative to

sending a standard card asking for a reprint. It is true that many requests for reprints are received from individuals who have not read the original paper when published and who are unlikely to make further use of a reprint, but I doubt whether many people do this sort of thing for long. Most requests for reprints probably come from those who are genuinely interested, and the others must be regarded as part of the price for the dissemination of new knowledge.

Stanley Royd Hospital,
Wakefield,
Yorkshire.

MAX HAMILTON.

SIR,—The experience of Dr. Faulds (Feb. 11) with requests for reprints is a familiar one. Years ago I received a request from a prominent specialist. In the medical library, one night soon afterwards, I diffidently approached the great man and thanked him for thus recognising my work. Both in manner and in word he let me know he had never heard of me. His secretary routinely sent postcard requests for reprints of all papers in his field.

In the 1930s I always enclosed a stamp with my letter requesting a reprint. Once, instead of the reprint, I got a card from the author asking for 15 or 20 cents, adding that his pay as a research-worker did not permit him to do otherwise. In forwarding the money I asked whether there was a difference between letter-writers and card-writers. There was: of about 18 letter-writers, almost all sent the money, while only a handful of the others, numbering 50 or 60, did so.

What is one to do? When requests for reprints are many and the supply is limited, only letters should be honoured. Card-writers should shift for themselves. Q.E.D.

Los Angeles,
California.

S. M. RABSON.

DIAGNOSIS OF HYPOFIBRINOGENÆMIA

SIR,—Dr. Aidin (Feb. 25) implies that chemical estimation of fibrinogen forms a reliable basis for the diagnosis of hypofibrinogenæmia in obstetric hæmorrhage.

In this condition clot formation may be obviously grossly defective and the thrombin time and titre quite abnormal, yet a chemical estimation of fibrinogen on the same specimen can give a normal result.[1] There is a discrepancy in these patients between "effective" fibrinogen, as measured by the thrombin test, and total fibrinogen, as estimated chemically. In addition, accurate biochemical measurement of fibrinogen in these cases is too lengthy a procedure, and the rapid ammonium-sulphate precipitation method is of doubtful accuracy.

In this condition there is no time to test for fibrinolysins, and the results of such tests do not help in the immediate diagnosis and treatment of the patient.

The diagnosis of this condition and the indication to treat immediately with an adequate infusion of fibrinogen should rest on observation of the clot and a thrombin time and titre test.[1 2]

St. Margaret's Hospital,
Epping, Essex.

P. D. ROBERTS.

DUPUYTREN'S CONTRACTURE

SIR,—In his letter (Feb. 4), Dr. Forgan mentioned that in his venereological practice he never found Dupuytren's contracture associated with Peyronie's disease.

Some workers, however, have noted a not infrequent coincidence of these conditions. I myself, in a series of 85 cases of Peyronie's disease, published in a Polish urological periodical (*Urologia Polska*),[3] described 8 cases associated with Dupuytren's contracture.

Leeds.

O. W. CINIEWICZ.

1. Sharp, A. A., Howie, B., Biggs, R., Methuen, D. T. *Lancet*, 1958, ii, 1309.
2. *Blood*, 1959, **14**, 1354.
3. Ciniewicz, O. W. *Urol. pol.* 1956, **9**, 179.

Obituary

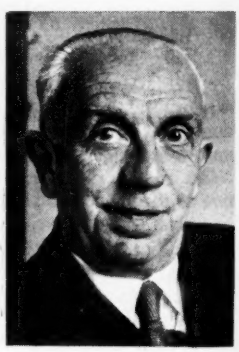
JOHN SEBASTIAN BACH STOPFORD
BARON STOPFORD OF FALLOWFIELD

K.B.E., Kt, M.D. Manc., Hon. Sc.D. Cantab. and Dubl., Hon. D.Sc. Leeds, LL.D. Manc. and Lpool, D.C.L. Durh., F.R.C.P., Hon. F.R.C.S., F.R.S.

THE honours, degrees, and titles which stand under Lord Stopford's name at the head of this column reflect the renown which he earned as neurologist, administrator, educationist, and statesman. His unofficial title of "prince of vice-chancellors" reflects the affection and admiration in which he was held by all who worked with him.

He was born in 1888 at Hindley Green, near Wigan, and his christian names were chosen by his grandfather, who was an organist at Upholland, but they failed to influence his development, for he later admitted that "a great symphony means no more to me than a tune on a barrel organ" and claimed the tin whistle as his only instrument, on which he was a defective performer. Instead at Manchester Grammar School and the University of Manchester he showed a bent for science, as well as for football, and he retained his taste for both.

Before qualifying in 1911 he was appointed to a university demonstratorship in anatomy and, after holding resident hospital appointments, he returned to the department to work under Grafton Elliot Smith. His classic studies of the blood-supply to the pons and medulla, for which he was awarded the M.D. and gold medal in 1915, already showed the practical and clinical bias which was to distinguish all his research. As one of his colleagues later put it, "Stopford has never been over interested in embryology as a general study, that Sahara that has desiccated so many of the anatomical schools of the world. What interested him in anatomy was the sick man, and the help that a more precise knowledge of structure could bring to explain his symptoms and to relieve his sufferings."



R. Lam-Po-Tang

The 1914–18 war gave him further clinical opportunities, and with a grant from the Medical Research Council he began to study gun-shot injuries of the peripheral nerves. Later he joined Mr. (now Sir) Harry Platt at the peripheral nerve injury centre which was established after the war at the Ministry of Pensions Hospital at Grangethorpe, and together they published an important series of papers. Stopford continued his studies on nerve injuries and compression for over fifteen years and they culminated in the publication of his book on *Sensation and the Sensory Pathway* in 1930. For this work he was elected F.R.S. in 1927.

During the war he had already become lecturer in anatomy at Manchester and in 1919 he succeeded Elliot Smith in the chair. With this appointment began his collaboration with Prof. E. D. Telford. They shared a variety of interests, ranging from diseases of the blood-vessels to the cultivation of auriculas, and to this period belong Stopford's studies of the sympathetic nervous system.

An outstanding gift for research does not always go with a talent for teaching. But Stopford was an ideal teacher—clear, simple, and brief. It was said that at least one reason why he became the youngest professor of anatomy in the country was that the students sent a deputation to the vice-chancellor asking for his appointment. Certainly Stopford took his responsibilities seriously, and ungrudgingly gave time to such academic "chores" as committee meetings, the deanship of the medical school, and the pro-vice-chancellorship of the university. In 1934, to the ill-concealed annoyance of his colleagues, who deplored his loss as an anatomist, he was persuaded to become vice-chancellor. Their forebodings were to some extent justified, for in 1937 he resigned from the chair of anatomy, and though he was appointed the same year to a personal chair of experimental neurology, inevitably the scientist gave way to the administrator. His success in this new sphere was the best compensation he could offer his colleagues. Before he retired in 1956 the number of students and staff in the university had doubled, and this expansion had been accomplished in a friendly and harmonious atmosphere, for Stopford had the gift of generating confidence and affection. His conduct of a committee, for instance, was masterly.

According to a fellow vice-chancellor's description "he never gives a committee the impression that his mind is made up and that its views are going to be superfluous. Instead he listens and observes, and if it is at all possible he draws the wise conclusion (which often he must have reached before coming to the meeting) out of some member of the committee. This facility for restraint, this reluctance to take the lead unless all your colleagues fail to take it, is a precious gift in academic administration."

Nor was his contribution to academic administration and medical education limited to Manchester.

He was a member of the General Medical Council, and chairman of its business committee, vice-chairman of the Goodenough Committee on medical schools, a member of the University Grants Committee, chairman of the Universities Bureau of the British Empire, vice-chairman of the Committee of Principals and Vice-Chancellors, vice-chairman of the trustees of the Nuffield Foundation, and the first chairman of the Manchester Regional Hospital Board.

His record of distinctions was appropriate to his record of service.

He held honorary degrees from half a dozen universities. He was elected F.R.C.P. under a special by-law. The Royal College of Surgeons gave him their honorary fellowship in 1955 at the first annual meeting of fellows and members to be held outside London. He was created a knight in 1941, K.B.E. in 1955, and became one of the first life peers in 1958.

J. M. Y. writes:

"My earliest recollections of Lord Stopford go back to my student days. At that time we were impressed by the excellence of Stoppie's teaching, and by his personal friendliness. After graduation, when I was working in the anatomy department as a research fellow, I began to know him in a different capacity. He was invariably both helpful and understanding, giving one the maximum of encouragement with the minimum of interference. But it was only when I returned to the department as assistant lecturer that I became able to appreciate to the full his manifold qualities of mind and character.

"He possessed a fund of common sense, and was always a very shrewd judge of people. He showed a flair for administration, and it became obvious at quite an early stage that his ability as an administrator would come to be more and more in demand as time passed. As anatomists we regretted his appointment to the vice-chancellorship. But our regret was tempered by the realisation that it was almost inevitable that he should be called upon to serve in a wider capacity, and his subsequent career demonstrated in no uncertain manner that what anatomy lost the university gained.

"When I left Manchester for Cardiff in 1932 we kept in regular contact with one another. Despite the numerous honours heaped upon him, he always remained as friendly and unaffected as when I first knew him—and still went regularly to football matches. In fact, despite both his knighthood and his peerage, I still find it hard to think of him as other than 'Stoppie'—and I like to feel that he too, knowing how affectionately that name was used, would have preferred it to any other."

R. W. L., a younger colleague, sends the following tribute from Manchester:

"After the first ten minutes of our first lecture in elementary anatomy—given in the small anatomy theatre of the Manchester Medical school in 1924—we very junior students knew that we had met a great teacher. The selection of essentials and the simple directness of presentation were hallmarks of an exceptionally clear mind. Later we learned without surprise that Stoppy had been appointed to the chair of anatomy at the age of 31 supported by a spontaneous petition from medical students. Many subsequent students would have supported the petition gladly (an honour which might not be accorded to all established professors). The clarity of mind we recognised in Stopford was wedded to a rare quality of heart, and the combination was the secret of his subsequent greatness as a vice-chancellor. He loved people *as* people. He was only too alert to our failures and inadequacies but he had the Christian's virtue of hating the fault and loving the man.

"The stress of the war years has shortened the lives of many non-combatants. Stopford's health suffered severely at that time and we were sometimes disturbed to see how haggard and spent he could be. Nevertheless, in 1947 he undertook to be first chairman of the Manchester Regional Hospital Board, an exacting but immensely creative post, and for this work both the few who know and the millions who are uninformed owe him a great debt of gratitude. His medical background, his grasp of essentials which could bring order out of chaos, and his rare human qualities made him the ideal man for this Herculean task.

"After he retired it was a privilege to visit him and Lady Stopford at their bungalow near Arnside. There he lived near enough to the main lines to London and to Manchester to be able, when he was sufficiently well, to take an active part in events. Although he knew well enough during the few years at Arnside that each day might be his last, he maintained his keen interest in national affairs, in the University, the Regional Hospital Board and the Board of Governors, and over a cup of tea he would discuss them with shrewd insight and humour.

"In losing Stopford Manchester has lost one of its greatest and most-loved men. It is not always that one can honestly use these adjectives in close proximity."

In 1916 Lord Stopford married Dr. Lily Allan, and they had one son. He died on March 6 at their home in Westmorland where they had settled after he retired from the vice-chancellorship in 1956.

The photograph is reproduced by permission of the editor of the *Manchester University Medical School Gazette*.

JAMES DAVIDSON

M.D. Edin.

Dr. James Davidson, who died on Feb. 15, was a medical missionary in India for some years and later practised in London and Edinburgh.

He was born in 1875 in Berwick-on-Tweed and was educated in Edinburgh at George Watson's College and the university, where he studied law and then medicine. During his medical course he was a student of the Edinburgh Medical Missionary Society, and after he qualified in 1903 he acted as

resident physician at the society's Livingstone Dispensary in the Cowgate. He went out as a medical missionary to Neyoor in South Travancore in 1905 and served there until he was forced by ill-health to retire in 1913. He settled in general practice in the South of England and later in Edinburgh, but he continued to take an active interest in all missionary work, especially in that of the London Missionary Society and the Edinburgh Medical Missionary Society, of which he remained a director until his death. A medical friend writes with affection and respect of Dr. Davidson's " gentle old-world courtliness and the thoroughness of all his work which endeared him to patient and colleague alike ". Dr. Davidson is survived by his widow, a daughter, and a son, Dr. J. Romanes Davidson, who is general director of the Quarrier's Homes and colony for epileptics at Bridge of Weir.

Diary of the Week

MARCH 19 TO 25

Monday, 20th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. R. I. S. Bayliss: Treatment of Œdema.

KING'S COLLEGE LONDON, Strand, W.C.2
5.30 P.M. Dr. S. J. Sarnoff (National Heart Institute, Bethesda): Homeometric Autoregulation in the Heart. (First of two Halliburton lectures in physiology.)

HUNTERIAN SOCIETY
7.30 P.M. (Talbot Restaurant, London Wall, E.C.2.) Sir Wilfrid Sheldon, Prof. D. V. Hubble: Educational Problems in Children.

Tuesday, 21st

KING'S COLLEGE LONDON
5.30 P.M. Dr. Sarnoff: Activity Graded Sympatholysis in the Vascular Bed Supplying Muscles. (Second of two Halliburton lectures in physiology.)

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.30 P.M. *Pathology*. Dr. J. N. Hunt, Dr. A. H. James: Physiological and Clinical Assessment of Gastric Function.

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. J. A. Dudgeon: Virus Infections. (Second of two lectures.)

CHARING CROSS HOSPITAL, W.C.2
6 P.M. (Medical School) Prof. H. H. Ussing (Copenhagen): Physiological Significance of Active Sodium Transport.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W.1
5.30 P.M. Mr. M. A. Bennett: Stereotaxis.

MANCHESTER MEDICAL SOCIETY
4.30 P.M. (Medical School, University of Manchester.) Sir John Charles: Theodore de Mayerne, Archiater.

Wednesday, 22nd

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Mr. Ashton Miller: Prevention of Infection in Urology.

ROYAL SOCIETY OF MEDICINE
5 P.M. *Endocrinology*. Dr. Barbara Boucher, Dr. A. Stuart Mason, Dr. R. M. Ehrlich, Dr. Martin Hartog, Prof. T. Russell Fraser, Dr. W. R. Butt, Dr. A. C. Crooke, Dr. F. J. Cunningham: Immunological Assay of Pituitary Hormones.

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Prof. Thomas Symington: Nature of the Ætiology and Pathogenesis of Adrenocortical Lesions.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. W. Riddell: Anti-fungal Agents.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. Lynne Reid: Pathological Basis of Unilateral Transradiancy of the Lung.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W.1
3.30 P.M. Dr. M. E. M. Herford: Health of Young People in Industry.

MANCHESTER MEDICAL SOCIETY
4.30 P.M. (Medical School, University of Manchester.) *Medicine*. Dr. E. D. Gray: Developments in Diagnostic Radiology. (Presidential address.)

Thursday, 23rd

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Mr. W. B. Jennett: Epilepsy after Blunt Head Injury. (Hunterian lecture.)

INSTITUTE OF NEUROLOGY, Queen Square, W.C.1
5.30 P.M. Prof. Vernon B. Mountcastle (Johns Hopkins University School of Medicine, Baltimore): Functional Meaning of Duality in the Somatic Afferent System.

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
4.30 P.M. (Chelsea Hospital for Women, Dovehouse Street, S.W.3.) Prof. Lee Buxton (Yale): Postcoital Test and Treatment of Male Infertility. (Fifth of six lectures.)

Friday, 24th

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
5.30 P.M. Mr. E. J. Radley-Smith: Brain Abscess.

Saturday, 25th

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
11.15 A.M. (Hammersmith Hospital, Ducane Road, W.12.) Professor Buxton: Treatment of the Abnormal Fallopian Tube in Infertility. (Last of six lectures.)

Notes and News

COMMUNITY CARE IN SCOTLAND

LAST May the Standing Advisory Committee on Local Authority Services of the Scottish Health Services Council was asked to consider how the authorities' mental-health services should be developed to meet their new responsibilities under the Mental Health Act. In its report [1] the committee recommends expansion to the point " at which no person need be resident in hospital unless he will benefit from or requires hospital care ". To translate this general aim into precise figures the authorities need more facts, and the committee urges that they should without delay set on foot a survey of the numbers of mentally disordered people in their areas and estimate the numbers likely to need each service. But the committee is anxious that evident need should not wait on figures. Among the services which it considers authorities should provide are friendly and informal home visits and advice for mentally handicapped children and adults who need supervision; more training and occupation centres for children excluded from ordinary schools, for mentally handicapped young people who need some extra training on leaving school, and for adults who cannot enter ordinary employment; and support for patients returning home from hospital. Discussing the extent to which authorities should provide homes and hostels for patients at present in hospital, the committee points out that estimates of those who could be discharged if alternative accommodation were available vary widely. At this stage authorities should probably concentrate on providing enough accommodation to meet the needs of mental defectives in the community, but should plan, in consultation with the hospitals, to relieve the hospital service in due course, either by providing more accommodation or by taking over some existing hospital accommodation to use as hostels. The committee adds, however, that where patients need constant and close supervision and are incapable of taking any significant part in the life of the community, there seems to be no advantage in transferring them from hospital to hostel. The committee hopes that all local authorities will recognise that they must allot adequate finance to the work, though shortage of trained staff, which cannot be quickly remedied, is bound to limit it at first. Measures to help the mentally handicapped and convalescent to enter ordinary employment, and measures to support those looking after these people in the home should receive priority over the more long-term task of providing accommodation for those in hospital who have no suitable home of their own in the community.

WHAT THE STUDENT THINKS

THE Association for the Study of Medical Education (ASME) has recently sent a questionary to 12,000 medical students, asking them questions about their attitudes and approaches to medicine and their medical education. This is the first time that information of this sort has been systematically collected, although the British Medical Students' Association has carried out valuable research into some aspects of the medical curriculum.

In this new inquiry, the Edinburgh research group of ASME have set out to determine the ways in which the attitudes of students with different ambitions and interests react to the processes of medical education. It is hoped that this will bring about an improved understanding of medical students and their problems and will shed light on the effects of medical education on those who receive it. The questionary is well designed and provides ample scope for students to express their views. Some of the questions inquire fairly deeply into the student's response to his work and will, perhaps, raise issues which the student will not have thought much about: it is not easy, for example, to select the five most important characteristics of a good doctor from the list of twenty-five that is provided. The analysis of the journals that students

1. Mental Health Services of Local Health Authorities. H.M. Stationery Office. Pp. 34. 1s. 9d.

read and refer to might also expose an interesting state of affairs. Another telling question asks what the student expects to earn by the time he is forty. The ways in which this figure correlates with the student's background and expressed ambition may well give an illuminating view of the different branches of medicine.

The answers to the questions are completely confidential so that students can speak freely: their answers have important bearings on the future of the medical curriculum.

HÆMOPHILIA SCHEME CENTRES

In 1954 a number of hospitals agreed, in collaboration with the Medical Research Council, the Ministry of Health, and the Department of Health for Scotland, to act as reference centres offering a registration service and diagnostic and treatment facilities for general practitioners with hæmophilic patients. The number of these centres has gradually increased and there are now centres at:

Aberdeen—Prof. H. W. Fullerton, Department of Medicine, Foresterhill.
Belfast—Dr. M. M. Stevenson and Dr. M. G. Nelson, Department of Clinical Pathology, Royal Victoria Hospital.
Birmingham—Dr. M. J. Meynell, United Birmingham Hospitals, General Hospital.
Bradford—Dr. R. Turner, Royal Infirmary.
Bristol—Dr. A. B. Raper, Department of Medicine, Royal Infirmary.
Cambridge—Dr. F. G. J. Hayhoe, Hæmatology Clinic, Department of Medicine, Tennis Court Road.
Cardiff—Prof. H. Scarborough, Medical Unit, Royal Infirmary.
Carlisle—Dr. J. S. Faulds, Cumberland Pathological Laboratory, Cumberland Infirmary.
Derby—Dr. B. J. Leonard, Royal Infirmary.
Dundee—Prof. R. B. Hunter, Department of Pharmacology and Therapeutics, Medical School, Queen's College.
Edinburgh—Dr. R. H. Girdwood, Department of Medicine, University New Buildings.
Exeter—Dr. J. O. P. Edgcumbe, Department of Pathology, Royal Devon and Exeter Hospital.
Glasgow—Prof. L. J. Davis, Department of Medicine, Royal Infirmary.
Hull—Dr. A. J. Shillitoe, Royal Infirmary; Dr. L. S. Sacker, Department of Pathology, Kingston General Hospital.
Leeds—Dr. W. Goldie, St. James's Hospital.
Liverpool—Dr. T. Black, Liverpool Royal Infirmary, Pembroke Place.
London—Dr. R. M. Hardisty, The Hospital for Sick Children, Great Ormond Street, W.C.1; Prof. J. V. Dacie, Postgraduate Medical School, Ducane Road, W.12; Dr. H. B. May, London Hospital, E.1; Dr. W. M. Davidson, King's College Hospital, S.E.5; Dr. G. I. C. Ingram, St. Thomas's Hospital, S.E.1; Dr. C. A. Holman, Lewisham Hospital, S.E.13; Dr. Bodley Scott, St. Bartholomew's Hospital, E.C.1.
Manchester—Dr. J. F. Wilkinson, Department of Hæmatology, Royal Infirmary.
Newcastle upon Tyne—Dr. H. Boon, Royal Victoria Infirmary.
Oxford—Dr. R. G. Macfarlane, Radcliffe Infirmary.
Portsmouth and I.O.W.—Dr. J. R. O'Brien, Central Laboratory, Milton Road, Portsmouth.
Sheffield—Dr. E. K. Blackburn, United Sheffield Hospitals, Department of Hæmatology, Royal Infirmary.

ADDISON IN AN UNFAMILIAR ROLE

THE name of Thomas Addison is so closely linked with his description, in 1849, of "a very remarkable form of general anæmia" that some other aspects of his work are often overlooked. To mark the centenary of his death, a special number of *Guy's Hospital Reports* has been devoted to him, and we are reminded [1] that in 1839 he was jointly responsible, with Bright, for an early and very accurate description of appendicitis. He was also one of the first men in this country to develop a special interest in dermatology, inculcated in part at the Lock Hospital, where he served his first London house-appointment, and in part by Thomas Bateman, whom he assisted at the Public Dispensary in Carey Street. Bateman was at that time completing the magnum opus *On Cutaneous Diseases* of his own teacher, Robert Willan, a treatise destined to make its authors internationally famous and which virtually founded a new specialty.

With such a training Addison might well have decided to devote himself to the study of skin diseases, though it would have been a difficult and impecunious career. (As Moynahan [2] remarks, it is significant that the first whole-time dermatologist in this country was Erasmus Wilson, who had ample private means and had qualified as a surgeon.) Instead Addison pursued a more orthodox course; but when he was eventually elected to Guy's his duties included those of Physician for Diseases of the Skin—an office in which such men as Hilton Fagge and Pye Smith succeeded him.

While he was at the hospital he built up, with the help of a very gifted artist, Joseph Towne, a unique collection of models depicting various skin diseases, which is used for teaching purposes to this day. During his later years he wrote,[3] with Gull, an original description of vitiligoidea, now called xanthoma, and appreciated that the condition was a cutaneous manifestation of a metabolic disorder. He also described [4] a circumscribed form of scleroderma, without realising that it had previously been reported on the Continent.

Addison developed a substantial private practice in dermatology but, like the rest of his practice, it was not very lucrative. Garrison considers that he was limited by "a haughty repellent manner which, on his own showing, concealed excessive shyness and sensibility." This may be so, but before dismissing him as a financial failure, it is worth noting that, at a time when the value of money was at least four times as great as it is today, he left £60,000.

1. Brock, R. *Guy's Hosp. Rep.* 1960, **109**, 273.
2. Moynahan, E. J. *ibid.* p. 262.
3. Addison, T., Gull, W. *ibid.* 1851, **14**, 265.
4. Addison, T. *Med. Chir. Trans.* 1854, **37**, 27.

University of Cambridge

The Milk Marketing Board and Private Centres Group are to give £32,000 so that the Mary Marshall professorship of the physiology of reproduction, which has been established for the tenure of one professor, may be converted into a permanent chair with the title Mary Marshall and Arthur Walton professorship.

University of Wales

The title of reader has been granted to Dr. F. Jacoby, senior lecturer in histology in the department of anatomy of the University College of South Wales and Monmouthshire.

Royal College of Physicians of London

Prof. L. J. Witts will give the Lumleian lectures on Tuesday and Thursday, April 11 and 13, at 5 P.M., at the college, Pall Mall East, S.W.1. His subject will be some aspects of the pathology of anæmia.

Royal College of Surgeons of England

At a meeting of the council on March 9, with Sir Arthur Porritt, the president, in the chair, Mr. R. L. G. Dawson was appointed adviser in training in plastic surgery, and Mr. W. A. Lisle Thompson was appointed Robert Jones travelling research fellow.

A diploma of membership was granted to E. J. W. Gumpert.

The council agreed, at the request of the Government of Pakistan, to hold a primary F.R.C.S. examination in Lahore in January, 1962.

Faculty of Anæsthetists.—on March 8 Prof. T. D. Gray was re-elected, and Dr. J. D. Roberston and Dr. C. F. Scurr were elected, to the Board of the Faculty.

Mental After Care Association

The annual general meeting of this Association will be held on Thursday, March 23, at 3 P.M., at the Hall of the Haberdashers' Company, Staining Lane, London, E.C.2. The speakers will be Rabbi Israel Brodie and Dr. J. C. Sawle Thomas.

Younghusband Report and Local Authorities

In a circular (10/61) commending the recommendations of the Younghusband Committee to local authorities, the Ministry of Health announces that new courses for general training in social work of the kind proposed in the report are to be started in advance of legislation at three colleges of further education. London County Council North-Western Polytechnic, City of Birmingham College of Commerce, and Liverpool College of Commerce are planning two-year full-time courses to begin in September, 1961. The National Council for Social Work Training when it is set up will be able to recognise them as leading to its certificates. It is hoped that authorities will be prepared to support the applications of suitable officers and to release, on full salary, any officer accepted by the college authorities.

International Congress on Mental Health

This congress is to be held from Aug. 30 to Sept. 5 in Paris. Further particulars may be had from the World Federation for Mental Health, 19, Manchester Street, London, W.1.

Medical Society of London

The statutes prescribed for this famous society by John Coakley Lettsom, the Quaker physician and philanthropist who founded it in 1773, still largely govern its activities; and he would have approved of the genial tradition that has made the society's anniversary dinner one of the most popular of London's medicosocial occasions. At the 181st dinner on March 9 Mr. Nils Eckhoff, the president, recalled that the original 1773 subscription of 1 guinea was still in force when he became a fellow, though (like most other subscriptions) it had had to be raised since. Mr. Eckhoff was able to record for the society a year of profitable activity, and he referred with particular pleasure to Major-General W. R. M. Drew's Lettsomian lectures on Plague and Pestilence. The President was replying to Mr. Justice Salmon's toast of The Society (" its annals coruscating with famous names "). Dr. Joseph Smart gave a warm welcome to The Guests. In a brief response Mr. Arthur Bell, F.R.C.O.G., said he had been looking at a record of a meeting of the society soon after the 1914–18 war at which his uncle, Blair Bell, spoke about the treatment of malignant disease with injections of colloidal gold. The plain account of the proceedings did not recapture the electric atmosphere sensed by those present, many of whom were still able to recall vividly this classic of medical controversy.

Refrigerated Ventilation for Operating-theatres

The Ministry of Health has expressed the opinion that refrigeration plant in operating-theatres cannot be justified for general use in the conditions normally encountered in this country. The planning and general purposes committee of the North West Metropolitan Regional Hospital Board has reported that, though in schemes for new operating-theatre suites the practice has been to allow space for such plant, the Ministry has hitherto approved its installation only in theatres where neurosurgery is to be undertaken. The committee suggests that the Ministry should reconsider its policy and agree to the installation of refrigeration equipment in new schemes and also, where possible, in existing operating-theatre suites where, because of heavy and continuous use, heat is built up heavily.

Trial of Disposable Syringes

A trial of disposable sterile plastic syringes at Edgware General Hospital has been approved by the North West Metropolitan Regional Hospital Board. The senior administrative medical officer reported that the other two chief methods of providing a sterile syringe service were: (1) for the hospital staff to undertake this work (a method already practised at some of the Board's hospitals, but in some areas difficult to initiate without new building); and (2) commercial provision of sterile syringes and needles (this method is being tried at Barnet General Hospital, where hitherto it has not proved entirely satisfactory). At present only 2 ml. disposable sterile syringes are to be had, and therefore Edgware General Hospital will have to supply its own sterile syringes of other sizes.

Photography on Expeditions

Doctors interested in photography who have been, or plan to go, on expeditions will be welcome at a 3-day symposium to be held jointly by the Scientific and Technical Group of the Royal Photographic Society, the Royal Geographical Society, and the British Association for the Advancement of Science, at the Royal Geographical Society, 1, Kensington Gore, London, S.W.7, on April 11–13.

The subject of photography on expeditions will be discussed under four headings: photography in special environments; function of photography on scientific expeditions; technical policy; finally, films and photographs will be shown to illustrate special problems. Programmes can be obtained from Mr. A. G. Tull, Technicolor Ltd., Bath Road, West Drayton, Middlesex.

A Joint Research Unit

The North West Metropolitan Regional Hospital Board have agreed to join the Medical Research Council in setting up a research unit in the department of gastroenterology at the Central Middlesex Hospital.

The unit will be set up for five years in the first instance under the direction of Dr. W. E. Rowlands, a member of the M.R.C. staff who already holds an honorary appointment at the hospital. The M.R.C. will provide accommodation and will meet the cost of staff salaries and expenditure on the research work of the unit. The Board will allocate 6 beds in the hospital to Dr. Rowlands, and junior hospital medical staff will provide clinical care for patients admitted to them.

Prof. Thomas Anderson is visiting Canada at the invitation of the Canadian Thoracic Society. He is to lecture to the branches of the society in Toronto, Winnipeg, Edmonton, and Vancouver, and in Vancouver he will also be guest speaker at the annual assembly of the Canadian College of General Practice.

Prof. R. Couteaux, who holds a chair of animal biology in the University of Paris, has been appointed to a Royal Society visiting professorship for 1961–62. He is expected to take up the appointment on Oct. 1, and to work in the department of biophysics at University College London on the structure and function of neuromuscular connections.

At a meeting of the Belmont Hospital Clinical Society on Thursday, March 23, at 8 P.M., Dr. John Cowie will speak on "the approved schoolgirl."

A meeting of the South Wales group of the British Geriatric Society will be held on Friday, March 24, at 8.30 P.M., in Cardiff, when Mr. D. A. Sanford will speak on surgery and geriatrics.

The National Association for Mental Health have published *A Letter to Parents of a Mongol Baby* from an anonymous children's specialist who works in a large maternity hospital. The letter is meant to be read by the parents during the first difficult weeks after they have been told about their baby, and it discusses with sympathy and simplicity the problems that they will have to face. Copies (1*s.* 3*d.*) may be had from the Association (Maurice Craig House, 39, Queen Anne Street, London, W.1).

Appointments

ADAM, CATHERINE K., M.B. Aberd., F.F.A. R.C.S., D.A.: consultant anæsthetist, East Fife hospital group.
COMPSTON, NIGEL, M.D. Cantab., F.R.C.P.: consultant physician, Royal Masonic Hospital, London.
CROSS, A. G., M.D. Cantab., F.R.C.S.: consultant ophthalmic surgeon, Royal Masonic Hospital, London.
JAMES, HERBERT, L.R.C.P.E., D.P.H.: deputy M.O.H. and deputy principal school M.O., Blackpool.

Manchester Regional Hospital Board:

BAIJAL, B. N., M.B. Agra, L.M.S.S.A., F.R.C.S.: senior casualty officer, Westmorland County Hospital, Kendal.
BROWN, R. H. L., M.B. Manc.: senior casualty officer, Ashton-under-Lyne General Hospital.
HALL, M. H., M.R.C.S.: senior casualty officer, Preston Royal Infirmary.
HAY, DAVID, M.B. Belf., M.R.C.O.G.: consultant obstetrician and gynæcologist, North Manchester hospital group.
POLLER, LEON, M.D. Manc.: consultant pathologist, South Manchester hospital group.
SHARP, JAMES, M.D. Manc., M.D. Rochester, N.Y., M.R.C.P.: consultant physician, Stockport, Buxton, and South Manchester hospital group.
WILKS, JOHN, M.B. Lond., F.R.C.S.: consultant general surgeon, Bolton and district hospital group.

Northern Regional Hospital Board, Scotland:

KINNEAR, PETER, M.B. St. And., F.R.C.S.E.: consultant surgeon, Lawson Memorial Hospital, Golspie.
MCLELLAN, D. M., M.B. Aberd., D.P.H.: assistant S.M.O., headquarters staff.
MELROSE, A. G., M.D. Glasg., M.R.C.P.E., F.R.F.P.S.: consultant physician, main duties at Royal Northern Infirmary and Raigmore Hospital, Inverness.

Western Regional Hospital Board, Scotland:

MACDONALD, I. R., M.B. Glasg., M.R.C.O.G.: consultant obstetrician and gynæcologist, Lanarkshire area maternity service.
STRANG, ROBERT, M.B. Glasg., F.R.C.S.E.: senior casualty officer, Stirling Royal Infirmary.
TAIT, A. M., M.B. Glasg., D.P.H.: administrative M.O.

Births, Marriages, Deaths

BIRTHS

PARRY.—On Feb. 7, at the Cardiff Maternity Hospital, to Winifred Margaret (formerly Bowen), B.SC., wife of Dr. T. E. Parry, M.R.C.P., of Dinas Powis, Glamorgan—a son.